DRUG:	WVE-003
STUDY NUMBER(S):	WVE-003-001
PROTOCOL(S) TITLE:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-003 Administered Intrathecally in Patients With Huntington's Disease
EUDRACT NUMBER:	2020-004556-15
SPONSOR:	**Wave Life Sciences USA, Inc** (for US) 733 Concord Avenue Cambridge, MA 02138 United States of America **Wave Life Sciences UK Limited** (for all other Ex-US) 1 Chamberlain Square CS, Birmingham, B3 3AX, United Kingdom
PROTOCOL AMENDMENT DATE:	26 December 2022
PROTOCOL AMENDMENT NO., VERSION NO.	Amendment 4.0 (Version 5.0)

CONFIDENTIAL INFORMATION

[redacted]

CLINICAL PROTOCOL APPROVAL FORM

SPONSOR: WAVE LIFE SCIENCES

I have read and understand the contents of this clinical protocol for Study No. WVE-003-001 dated 26 December 2022 (Amendment 4.0) and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

[redacted] **Date**

Medical Director, Clinical Development
Wave Life Sciences

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. WVE-003-001 dated 26 December 2022 (Amendment 4.0) and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current International Conference on Harmonisation guidelines governing Good Clinical Practices, applicable Food and Drug Administration (FDA) regulations, and other local regulatory requirements:

Name of Principal Investigator:

Title:
Institution:

Address:
Phone:
Fax:

Signature	**Date**

PROTOCOL SYNOPSIS

Sponsor: Wave Life Sciences Ltd.	**Investigational Product:** WVE-003	**Developmental Phase:**	**EudraCT Number:**

Title of Study: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-003 Administered Intrathecally in Patients With Huntington's Disease

Protocol Number: WVE-003-001

Study Center(s): Approximately 30 study centers

Objectives:

Primary objective:

- To evaluate the safety and tolerability of WVE-003 in patients with Huntington's disease (HD)

Secondary objectives:

- To characterize the pharmacokinetics (PK) of WVE-003 in plasma
- To characterize the concentration of WVE-003 in cerebrospinal fluid (CSF)

Exploratory objectives:

- To evaluate the pharmacodynamic (PD) effect of WVE-003 on the levels of mutant huntingtin (mHTT) protein in CSF
- To evaluate the effect of WVE-003 on clinical measures of disease including the Unified Huntington's Disease Rating Scale (UHDRS) and Short Problem Behaviors Assessment (PBA-s)
- To evaluate the PD effects of WVE-003 on relevant biomarkers in CSF, plasma, and peripheral blood mononuclear cells (PBMCs) (e.g., levels of wild type huntingtin [wtHTT] protein and total huntingtin [tHTT] protein in CSF and neurofilament light [NfL] in CSF and plasma)
- To evaluate changes from baseline in magnetic resonance imaging (MRI) of the brain

Methodology: This is a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of WVE-003 in adult patients with early manifest HD who carry the targeted single nucleotide polymorphism (SNP) rs362273 (SNP3).

To participate in the study, patients must undergo prescreening to confirm they are heterozygous for SNP3 with the A variant on the same allele as the cytosine-adenine-guanine (CAG) triplet expansion. Prescreening can happen any time before Screening. The prescreening testing process to confirm the presence of SNP3 is expected to take up to 6 weeks. If patients meet these criteria, they will continue to the Screening visit. The prescreening assessment will have a separate informed consent form (ICF).

The study will include 2 distinct periods: Period 1 to evaluate single ascending dose (SAD) cohorts and Period 2 to evaluate multiple ascending dose (MAD) cohorts of WVE-003. **Period 2 will not be initiated until this Substantial Amendment to the Investigational Medicinal Product Dossier (IMPD) with the supportive nonclinical data is approved by the local regulatory authorities. Following this approval, the Sponsor intends to initiate Period 2.** Patients may participate in Period 1 (SAD) and Period 2 (MAD) or Period 2 (MAD) only. All patients enrolled in Period 1 cohorts will have the opportunity to receive multiple doses in Period 2.

Sponsor: Wave Life Sciences Ltd.	**Investigational Product:** WVE-003	**Developmental Phase:**	**EudraCT Number:**

Cohorts in both Period 1 and Period 2 will be enrolled, randomized, and dosed in a sequential manner. Subsequent cohorts will not initiate until the requirements for dose escalation are met (as defined below). This study will utilize both a Dose Escalation Committee (DEC) and a Safety Monitoring Committee (SMC). The DEC will be responsible for making recommendations regarding dose escalation in Period 1, initiation of multiple dosing in Period 2, and subsequent dose escalation in Period 2. Decisions made by the DEC will be reviewed by the SMC, which makes the final recommendation.

WVE-003 will be administered intrathecally in a volume of 20 mL of artificial CSF (aCSF).

Period 1:

Period 1 will evaluate SAD cohorts of WVE-003. The planned Period 1 dose cohorts were as follows. Dose and cohort sizes were modified following recommendations from the DEC and SMC (details provided in Section 2.3).

- Period 1 Cohort 1 (P1C1): 6 patients (2:1 active:placebo); 30 mg
- P1C2: 6 patients (2:1 active:placebo)

If the DEC or the Sponsor determines additional single-dose data are required prior to initiating Period 2, subsequent SAD cohorts may be conducted.

The first 2 patients (1:1 active:placebo) in Period 1 cohorts will be dosed and observed for 2 days in the clinic. If neither of these sentinel patients experiences a serious adverse event (SAE) and the Single Dose Stopping Criteria (as defined below) are not met, the remaining patients will be dosed sequentially. Subsequent patients will be observed in the clinic for 1 day after dosing. Immediately after study drug administration, all patients should be ambulatory and active for approximately 30 minutes postdose. The Investigator should note any weakness or fatigue during this period. Formal physical examinations targeting the neurological system will be performed postdose. Any postdose SAEs will be monitored until resolution.

All patients will continue to be assessed for safety, PK, PD, and clinical effects through a minimum of 12 weeks. Prior to Period 2 initiation, patients will continue to attend monthly follow-up visits through Week 24. After Period 2 initiation, patients can proceed to multiple dosing in Period 2 if the Week 12 visit has been completed.

Subsequent SAD cohorts will not initiate until the requirements for dose escalation are met (as defined below).

In addition, pending approval from local regulatory authorities of nonclinical data supportive of multiple dosing to initiate Period 2, the DEC and SMC will also determine if patients can proceed to multiple dosing in Period 2.

Period 2

Patients in Period 2 Cohort 1 (P2C1) will receive 30 mg WVE-003 or placebo administered every 8 weeks (Q8W). Approximately 24 patients will be enrolled in P2C1. Dose levels and cohort sizes for Period 2 subsequent cohorts will be determined by the DEC/SMC based on previous Period 2 cohort data. [redacted]

All patients from Period 1 will have the opportunity to roll into Period 2 and will receive up to 3 additional doses of WVE-003 or placebo. Patients will not be re-randomized and will continue to receive active drug or placebo based on Period 1 treatment assignment. Patients will roll into the current Period 2 cohort, irrespective of Period 1 dose level.

Patients may be replaced in accordance with the requirements for dose escalation. Future DEC/SMC recommendations may include the addition of new Period 2 patients. All new patients in Period 2 will receive up to 3 doses of WVE-003 administered no more often than Q8W.

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P2C1 will be initiated pending approval from local regulatory authorities of nonclinical data supportive of multiple dosing to initiate Period 2, in addition to DEC and SMC approval. Subsequent MAD cohorts (P2C2 and P2C3) will initiate when the requirements for dose escalation are met (as defined below).

Immediately after study drug administration in any cohort, all patients should be ambulatory and active for approximately 30 minutes postdose on all dosing days. The Investigator should note any weakness or fatigue during this period. Formal physical examinations targeting the neurological system will be performed postdose on all dosing days. Any postdose SAEs will be monitored until resolution. Patients will attend clinic visits every 4 weeks (Q4W) for assessments of safety, PK, and PD. Patients in P2C1 will receive doses on Week 0, Week 8, and Week 16. Pending DEC/SMC recommendation, subsequent cohorts may receive doses Q8W or less frequently (e.g., on Week 0 and Week 12). Patients will continue to be assessed for safety, PK, PD, clinical effects, and MRI through a minimum of 12 weeks after their last dose.

Dose Escalation Committee Review

The DEC will be responsible for making recommendations regarding dose escalation in Period 1, selection of the initial dose level in Period 2, and subsequent dose escalation in Period 2.

Period 1 Dose Escalation: After all patients in a Period 1 cohort have received study drug and completed 2 weeks of postdose follow-up, the DEC will review the available safety and PK data. The DEC will determine if it is safe to proceed with the next SAD cohort. [redacted]

Initiation of Period 2: The DEC will review the available safety and PK data and decide if Period 2 (i.e., P2C1) can be initiated. Note that P2C1 will not be initiated until repeat-dose toxicity data have been submitted to and approved by the local regulatory authorities.

Period 2 – Subsequent MAD Cohorts (P2C2 and P2C3): Once 6 patients in the current cohort have received at least 2 consecutive doses, the DEC will review the available safety and PK data and determine if it is safe to proceed with the subsequent multiple-dose cohort. The DEC may also choose to reduce the number of doses in a cohort or reduce frequency of dose administration based upon their review.

Based on data review, the DEC may decide to add additional cohorts in either Period 1 or Period 2, select alternate dose levels (including lower doses) for any of the cohorts, or change the number of patients planned for a cohort. [redacted]

The DEC will review blinded data. All recommendations of this committee will be reviewed by the SMC, which makes the final recommendation.

Safety Monitoring Committee Review: In addition to reviewing the DEC's decisions, the SMC will review unblinded aggregate safety data periodically and on an ad hoc basis throughout the study. The SMC will review any SAEs that occur in sentinel patients in order to determine if the cohort should continue or if a lower dose should be selected. In addition, if treatment-emergent adverse events (TEAEs) occur that meet the Stopping Criteria, the SMC will review the unblinded safety data and determine whether it is safe to proceed with the cohort or if a lower dose should be explored.

If the stopping criteria are met at any point in the study, enrollment and dosing will be suspended until the data are reviewed. Similarly, if an SAE occurs in the sentinel patients in a cohort, no additional patients will be dosed in that cohort until the safety data are reviewed.

Single Dose Stopping Criteria: During Period 1, dosing of patients in a cohort will be suspended:

- If a single patient experiences an SAE assessed as related to study drug;

Sponsor: Wave Life Sciences Ltd.	**Investigational Product:** WVE-003	**Developmental Phase:**	**EudraCT Number:**

- If 2 patients experience a severe TEAE that is assessed as related to study drug; or
- If 4 patients experience a non-serious moderate or severe TEAE within the Medical Dictionary for Regulatory Activities (MedDRA) High Level Group Term (HLGT) *Spinal cord and nerve root disorders*, assessed as related to study drug.

Notification of dose suspension for a given cohort will be made in accordance with applicable regulations. If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations (e.g., substantial amendment) prior to restarting treatment.

Period 2 Stopping Criteria: During Period 2, either of the following will result in a dosing halt within the cohort and trigger assessment by the SMC to decide the safe dose level in Period 2:

- If 2 patients in a cohort experience an SAE assessed as at least possibly related to study drug.
- If 2 patients in a cohort experience a non-serious severe TEAE assessed as at least possibly related to study drug.

In addition, dosing will be stopped in any ongoing higher dose cohorts if the stopping rule is met in a lower-dose Period 2 cohort.

Notification of dose suspension for a given cohort will be made in accordance with applicable regulations. If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations (e.g., substantial amendment) prior to restarting treatment.

Individual Stopping Criteria: Dosing will be stopped for an individual patient at any time in the study if:

- A patient experiences a serious or intolerable adverse event (AE) that, in the Investigator's opinion, requires study drug discontinuation.
- A patient experiences a TEAE that is severe in intensity and related to administration of WVE-003 (except those TEAEs associated with lumbar puncture).

The patient will be followed up for safety per protocol. Per the Investigator's judgement, the patient may be allowed to resume participation in the study if or when the event has resolved. Dosing may be resumed for individual patients upon recovery from the severe event and if supported by the Investigator, based on their assessment of the benefit/risk balance for the patient.

Adverse event terms related to lumbar puncture and administration (e.g., procedural pain, traumatic lumbar puncture, or post-lumbar puncture syndrome) will be exempted from the assessment of Stopping Criteria. A full list of AE terms exempt from the Stopping Criteria is provided in Section 4.4.3.4.

Number of Patients (Planned): Approximately 54 patients

Study Population: Patients must satisfy all of the inclusion and none of the exclusion criteria to be eligible for the study. Patients will be required to be prescreened to determine heterozygosity at SNP3 with the A variant only on the same allele as the CAG triplet expansion.

Inclusion Criteria:

1. Documented ability to understand the written study ICF(s) and consent and has provided signed written informed consent prior to any study procedures
2. Ambulatory male or female
3. Age ≥25 to ≤60 years old
4. Body mass index (BMI) ≤32 kg/m^2
5. Documented CAG triplet repeats ≥36 in the *HTT* gene

Sponsor: Wave Life Sciences Ltd.	**Investigational Product:** WVE-003	**Developmental Phase:**	**EudraCT Number:**

6. Documented heterozygosity at SNP3
7. Documented presence of the A variant of SNP3 on the same allele as the pathogenic CAG triplet expansion
8. Clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4
9. UHDRS Total Functional Capacity (TFC) scores ≥9 and ≤13
10. In the opinion of the Investigator, the patient is able to tolerate all study procedures, and is willing to comply with all other protocol requirements.
11. Willingness to practice highly effective contraception for the duration of the study and for [redacted] after the last dose of study drug, if patients or their partners are of childbearing potential. Non-childbearing potential and highly effective methods of contraception are defined in the protocol. In addition, willingness to forego sperm or ova (egg) donation for the duration of the study and [redacted] months after completion of the study.

Exclusion Criteria:

1. Malignancy or received treatment for malignancy, other than treated basal cell or squamous cell carcinoma of the skin, within the previous 5 years
2. Positive for Hepatitis B virus (HBV) or Hepatitis C virus (HCV).
3. Known to be positive for human immunodeficiency virus (HIV).
4. Clinically significant medical finding on the physical examination other than HD that, in the judgment of the Investigator, will make the patient unsuitable for participation in and/or completion of the study procedures
5. Previously received tominersen
6. Received prior treatment with viral or cellular-based gene therapy
7. Received any other study drug, including an investigational oligonucleotide, within the past 1 year or 5 half-lives of the drug, whichever is longer, with the exception of the following:
    a. Received WVE-120101 within the last 3 months (i.e., 5 half-lives); or
    b. Received WVE-120102 within the last 3 months (i.e., 5 half-lives)
8. Implantable central nervous system device that may interfere with ability to administer study drug via lumbar puncture or undergo MRI scan
9. History of substance abuse disorder (except nicotine) within 6 months prior to the Screening Visit
10. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit
11. Started or changed dose for concomitant medication for the treatment of HD symptoms or psychiatric disorders within 30 days prior to the Screening Visit (concomitant medications that have been administered on a stable regimen for ≥30 days are permitted)
12. Pregnant (as determined by a serum pregnancy test) or breast feeding at the Screening Visit, or plans to become pregnant during the course of the study
13. Clinically significant laboratory abnormality at Screening
14. Clinically significant abnormality at Screening electrocardiogram (ECG), including but not necessarily limited to a confirmed QT interval corrected for heart rate (QTc) ≥450 msec for males or ≥470 msec for females

Sponsor: Wave Life Sciences Ltd.	**Investigational Product:** WVE-003	**Developmental Phase:**	**EudraCT Number:**

15. Clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal, neurologic, malignant, metabolic, psychiatric, or other condition that, in the opinion of the Investigator, precludes the patient's safe participation in the study or would interfere with the study assessments. Mental status, psychiatric medical history, and eligibility for the study must be documented in the screening questionnaire.
16. Bone, spine, bleeding, or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture
17. Inability to undergo brain MRI (with or without sedation)
18. Deemed to be at significant risk for suicidal behavior based on any the following criteria:
    a. The opinion of the Investigator
    b. Answers "yes" to Actual Suicide Attempts or Suicidal Behaviors in the Suicidal Behaviors section of the Columbia-Suicide Severity Rating Scale (C-SSRS) with reference to a 2-year period prior to the Screening Visit
    c. Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to the Screening Visit
    d. Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS at the Baseline Visit since the last visit (Screening Visit)
19. Involved directly or indirectly in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study
20. History of hypersensitivity to other antisense oligonucleotides and any other drug that in the opinion of the investigator may preclude study participation.

Investigational Product, Dose, Route, Regimen:

The currently planned starting dose level in Period 1 is 30 mg. The dose levels in subsequent Period 1 cohorts and Period 2 will be determined based on the findings in Period 1 and pending repeat-dose toxicity data from the GLP studies. [redacted]

WVE-003 will be provided as lyophilized powder for reconstitution and dilution for IT injection. WVE-003 for injection will be prepared by reconstituting and diluting the lyophilized powder with aCSF supplied by the Sponsor.

Reference Therapy, Dose, Route, Regimen:

Placebo will be aCSF provided by the Sponsor. It will be a sterile, preservative-free solution. Placebo will be visually identical in appearance to the WVE-003 injection solution and administered intrathecally in order to maintain the blind. Placebo will be administered in a volume of 20 mL.

Study Duration:

Period 1: This period will consist of a single dose and up to 24 weeks of postdose follow-up.

Period 2: This period will consist of up to 16 weeks of treatment and a minimum of 12 weeks of follow-up.

Endpoints:

Safety:

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Adverse events, concomitant medications, physical examinations including detailed neurological examination, vital signs, weight, 12-lead ECGs, clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis), CSF safety evaluations, MRI of the brain, and C-SSRS

Pharmacokinetics:

- Pharmacokinetic parameters of WVE-003 in plasma
- Concentration of WVE-003 in CSF

Pharmacodynamics:

- Change from baseline in the level of mHTT protein in CSF
- Change from baseline in the level of wtHTT protein in CSF
- Change from baseline in the level of tHTT protein in CSF
- Change from baseline in the level of NfL in CSF
- Change from baseline in the level of exploratory biomarkers in CSF, plasma, and/or PBMCs

Clinical Effects Endpoint(s):

- Change from baseline in the UHDRS TFC
- Change from baseline in UHDRS total motor score
- Change from baseline in the UHDRS independence scale
- Change from baseline in Symbol Digit Modalities Test
- Change from baseline in Stroop word reading test
- Change from baseline in the composite UHDRS
- Change from baseline in the PBA-s
- Changes from baseline in MRI of the brain

Statistical Methods:

The sample size was not calculated on the basis of statistical hypothesis testing; however, the number of patients is sufficient for a Phase 1b/2a assessment of safety, tolerability, PK, and early measures of PD and clinical effects.

Summary statistics (n, mean, standard deviation [SD], median, minimum and maximum values for continuous variables, and number [%] of patients in each category for categorical variables) will be provided by dose group and visit.

The change from baseline for PD and clinical effects endpoints will be summarized using a mixed model for repeated measures (MMRM). The MMRM will be used to construct 95% confidence intervals and to test for differences between dose groups and placebo.

Treatment-emergent AEs (TEAEs) and treatment-emergent SAEs will be summarized for each dose group based on MedDRA coding of verbatim terms reported by investigators.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
aCSF	artificial cerebrospinal fluid
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AS LR-PCR	allele-specific long-range polymerase chain reaction
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from 0 to 24 hours
BACHD	bacterial artificial chromosome (BAC)-mediated transgenic Huntington's disease
BMI	body mass index
CAG	cytosine-adenine-guanine
CBC	complete blood count
CE	capillary electrophoresis
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
DEC	Dose Escalation Committee
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EHDN	European Huntington's Disease Network

Abbreviation	Definition
EOS	end of study
ET	early termination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Huntington's disease
HED	human equivalent dose
HIV	human immunodeficiency virus
HLGT	High Level Group Term
HTT	Huntingtin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICV	intracerebroventricular
IMPD	Investigational Medicinal Product Dossier
IRB	Institutional Review Board
IRT	interactive response technology
IT	intrathecal
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mHTT	mutant huntingtin
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
NfL	neurofilament light
NOAEL	no-observed-adverse-effect-level
PBA-HD	Problem Behaviors Assessment for HD

Abbreviation	Definition
PBA-s	Short Problem Behaviors Assessment
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PT	Preferred Term
PxCx	Period x Cohort x
Q4W	every 4 weeks
Q8W	every 8 weeks
QTc	QT interval corrected for heart rate
RNA	ribonucleic acid
RP-PCR	repeat primed polymerase chain reaction
RSI	reference safety information
SAD	single ascending dose
SAE	serious adverse event
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SMC	Safety Monitoring Committee
SNP	single nucleotide polymorphism
SNP3	single nucleotide polymorphism rs362273
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TFC	Total Functional Capacity
tHTT	total huntingtin
$t_{1/2}$	half-life
t_{max}	Time of occurrence of C_{max}
UHDRS	Unified Huntington's Disease Rating Scale
wtHTT	wild type huntingtin

1 INTRODUCTION

1.1 Huntington's Disease

Huntington's disease (HD) is a rare, progressive neurological disease that results in motor, cognitive, and psychiatric disability and is invariably fatal[1]. Because it is a genetic, hereditary disease, it can affect multiple family members across generations[2]. Although cognitive and psychiatric symptoms may develop first, one of the most visually prominent symptoms of this disease is chorea. Chorea is an abnormal involuntary movement disorder, which occurs in 90% of patients and is moderate to severe in approximately 70% of these patients. These physical symptoms can appear at any age, but typically appear between the ages of 30 and 50 years[1]. A physical examination, sometimes combined with a neurological examination, can determine whether the onset of the disease has begun. Life expectancy after symptom onset is reduced to around 15 to 20 years[1,2]. As symptoms progress, individuals become increasingly or totally dependent on others for care. Suicidal ideation is increased in the early stages of the disease, likely associated with a perceived loss of independence, and patients with HD have a significantly higher rate of suicide as compared with a normal healthy adult population (138 per 100,000 and 12 to 13 per 100,000 persons per year, respectively)[3,4].

Prevalence in Europe, North America, and Australia is approximately 6 per 100,000[5]. Currently, no treatments exist that can cure, slow, or reverse the course of HD. Some of the symptoms of HD can be managed with medication and therapies such as antipsychotics and drugs affecting the dopamine pathways, which modulate the movement disorder[2].

Huntington's disease is caused by known mutations on a single gene, characterized by an expansion of a cytosine-adenine-guanine (CAG) triplet repeat in the *Huntingtin* (*HTT*) gene[6]. Wild type HTT (wtHTT) protein is critical for neuronal development[7]. Although the purpose of wtHTT in adults is not completely understood, it is believed to be a scaffolding protein that helps coordinate other proteins and cellular functions[8], and some studies have shown that it may play an important role in neuronal functions[7,9-11]. However, expansion in the CAG triplet repeat in the *HTT* gene results in production of the mutant huntingtin (mHTT) protein. Mutant HTT is thought to cause disease by a predominant toxic gain-of-function mechanism[8]. In nonclinical studies, lowering the level of mHTT protein as measured in the cerebrospinal fluid (CSF) has been demonstrated to be therapeutic[12,13]. Therefore, a drug that can silence the *mHTT* gene transcript while leaving the wild type allele intact may be able to slow, stop, or even reverse the course of HD[14].

1.2 Investigational Product WVE-003

WVE-003 is a stereopure antisense oligonucleotide (ASO) being developed to selectively target the *mHTT* transcript leaving the wtHTT transcript relatively unaffected. WVE-003 specifically targets the *mHTT* messenger RNA (mRNA) transcript at the A variant of single nucleotide polymorphism (SNP) rs362273 (SNP3). An SNP is a single nucleotide variation in the deoxyribonucleic acid (DNA) that can be associated with a mutated gene. One of the most frequent SNPs in the *mHTT* gene is SNP3, which has been shown to be present in approximately 40% to 45% of patients with HD[15,16]. By selectively targeting the SNP3 variant associated with

the pathogenic CAG expansion (≥36 repeats), treatment with WVE-003 should result in selective reduction of *mHTT* transcript and protein levels.

Oligonucleotides are a type of nucleic acid molecule synthesized from chemically modified ribonucleic acid (RNA) and/or DNA monomer building blocks[17,18]. WVE-003 contains phosphodiester and phosphorothioate internucleotide linkages, as well as a novel backbone chemistry: phosphoramidate linkages. Unlike phosphorothioate diester or phosphodiester linkages, which are both permanently negatively charged, the stereodefined phosphoramidate used in WVE-003 ([1,3-dimethylimidazolidin-2-ylidene] phosphoramidate diester) is not charged at physiological pH. It is hypothesized that charge modulation of ASOs could enhance cellular uptake[19,20].

1.3 Nonclinical Data

Based on the results of the nonclinical studies, WVE-003 has promise as a disease-modifying agent for the treatment of patients with HD. In vitro pharmacology studies confirmed that WVE-003 demonstrates selective knockdown of the mHTT mRNA and protein through cleavage of the mutant allele versus the wild type allele. This selective knockdown results in greater reduction of the mHTT protein over wtHTT protein produced by this RNA and, thus, may limit the unintended, potentially deleterious effects of decreasing wtHTT[7,9-11]. In vivo studies utilized the bacterial artificial chromosome (BAC)-mediated transgenic Huntington's disease (BACHD) transgenic mouse model, which demonstrated target engagement by dose-dependent reductions in HTT transcripts in the striatum and cortex after intracerebroventricular (ICV) administration of WVE-003 that was sustained for 12 weeks. The optimal dose and dosing frequency for efficacy in humans was modeled using data from the BACHD mouse and cynomolgus monkey and will be further explored during clinical development.

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[redacted]

1.4 Clinical Experience

This will be the first clinical study conducted with WVE-003.

2 RATIONALE FOR THE STUDY

This initial clinical study with WVE-003 was designed to evaluate the safety and tolerability of single ascending dose (SAD) cohorts followed by multiple ascending dose (MAD) cohorts. Information on the safety, tolerability, PK, pharmacodynamics (PD), and clinical effects of WVE-003 will inform dose selection for subsequent clinical studies.

As the primary endpoint is the safety and tolerability of WVE-003, placebo is the most appropriate comparator for this study. It is also important to distinguish between drug-related and procedure-related adverse events, which is difficult in a limited number of patients. Therefore, performing lumbar punctures in patients receiving placebo will be crucially important for comparison. Furthermore, one vital objective is to evaluate the biologic response to the study drug, which will be measured using mHTT levels in CSF. It is important to understand the natural variability in the level of mHTT in CSF within a single patient as well as between patients in order to accurately interpret these mHTT measurements. In addition to trying to establish whether or not mHTT lowering occurred, demonstration of dose response would be important in the planning of subsequent studies. Together with exposure data, mHTT lowering at different doses will form the basis of modeling to identify the optimal dose(s) and dosing interval in subsequent studies.

The volume of injection with artificial CSF (aCSF) is 20 mL, and an equivalent volume of CSF will be withdrawn for bioanalysis and to maintain CSF pressure. It is a relatively small volume compared to the total volume of CSF in humans, which is approximately 150 mL (range – 130 to 160 mL), with normal production rate of CSF being approximately 500 mL per day[28].

As this is a safety and tolerability study, HD patients who are in the early stages of disease, characterized by mild or no incapacity, will be selected in order to characterize the safety and tolerability of WVE 003. Early stage HD patients are capable of informed consent as evidence by their near normal functional capacity. It is necessary to conduct this study in patients, rather than in healthy volunteers, for 2 reasons. First, a better understanding of the safety and effects of WVE-003 in its intended target population will be achieved in patients because the intended target of WVE-003 is not present in healthy volunteers. Second, WVE-003 must be administered via IT administration, and consideration of the balance between risk and benefit justifies investigation in a patient population only. Although assessment of safety is the primary objective of this study, HD patients who enroll in this study will be relatively early in the manifest disease

process and may experience benefit from the investigational treatment if it addresses the primary pathogenesis of the disease.

Although evaluation of safety and tolerability is the primary objective of this study, HD patients who enroll in this study will be relatively early in the manifest disease process and may experience benefit from the investigational treatment if it addresses the primary pathogenesis of the disease.

Period 1 will evaluate the initial safety and tolerability of single doses of WVE-003. In an effort to enable patients to derive additional benefit through repeated exposure to WVE-003, all patients from the SAD part of the study (Period 1) will be allowed to roll into Period 2, during which they will receive up to 3 additional doses of WVE-003. Additional new patients may be enrolled directly into Period 2, which will evaluate multiple ascending dose (MAD) cohorts. Patients will have a minimum 12-week washout period between Periods 1 and Period 2. [redacted]

The follow-up in Period 1 was extended up to 24 weeks based on PK/PD analyses following single doses of WVE-003, after which mean reductions in CSF mHTT from baseline of 22% were observed. The extension of the follow-up period provides the opportunity to obtain additional plasma and follow-up imaging samples prior to participation in Period 2. Patients are only required to complete Period 1 Day 85 prior to rollover into Period 2.

This protocol details the complete study design and assessments to be performed in both Period 1 and Period 2. However, Period 2 of the study (multi-dose part) will not be initiated until this substantial amendment to the Investigational Medicinal Product Dossier (IMPD; or regional equivalent thereto) containing supportive repeat-dose toxicity data is approved by the local regulatory authorities. By taking this approach, it provides full transparency regarding the availability of repeat-dose exposure for patients enrolled in the SAD period of the study (Period 1) at the time of informed consent. In addition, this approach will help to minimize any gap between Periods 1 and 2 for patients enrolled in the SAD period. The Sponsor will communicate this approval (in writing) directly to the study sites for initiation of Period 2.

[redacted]

2.1 Rationale for the Doses and the Dosing Regimen

This study is designed to evaluate the safety, tolerability, PK, PD response, and clinical effect associated with WVE-003 and to support its further clinical development. The selection of the starting and subsequent doses and dose frequency was based on multiple factors, including projected human exposure and target engagement (mHTT mRNA knockdown) based on in vivo studies in animals, and the NOAEL provided by the GLP toxicity studies.

[redacted] [29-31]

This dose level is associated with a 5.6-fold safety margin based on the human equivalent dose (HED, based on CSF volume[29-31]) of the NOAEL observed in monkeys (15 mg; HED of 168 mg) and a 16.8-fold safety margin based on the HED of the NOAEL observed in rats (0.9 mg; HED of 504 mg). This dose was selected to adequately balance the risk/benefit for patients.

[redacted] The Sponsor reviewed available safety, tolerability, and PK data from prior dosed cohort(s) in Period 1 before selecting subsequent higher single doses for evaluation. Details on the criteria for dose selection are presented in Section 4.4.1.1.

Based on an unblinded review of available safety, PK, and PD data from Period 1, the Dose Escalation Committee (DEC)/Safety Monitoring Committee (SMC) recommended initiation of Period 2 with a dose level and frequency of 30 mg administered Q8W for Period 2 Cohort 1 (P2C1). WVE-003 showed an acceptable safety profile in HD patients who received a single dose of WVE-003 up to 90 mg in Period 1. In addition, the mHTT target engagement was observed following single doses of WVE-003, after which mean reductions in CSF mHTT from baseline of 22% were observed. Based on single dose PK in Period 1, 30 mg and Q8W dosing interval is projected to minimize potential drug accumulation while potentially enabling greater target engagement as compared to single dose. The total dose to be administered in P2C1 is 90 mg, equivalent to the highest single dose of 90 mg tested in Period 1, which appears to be safe and well tolerated. [redacted]

[redacted] Section 4.4.1.3 [redacted]

The Sponsor will continue to evaluate available nonclinical and clinical data to optimize the dose level and frequency in Period 2. WVE-003 will not be administered more frequently than Q8W through Week 16, for a maximum of 3 total doses.

2.2 Anticipated Benefit/Risk

Huntington's disease is a rare, progressive neurological disease[1]. Currently available treatments for HD only mitigate symptoms and do not affect the underlying HD pathology, the disease course, or life expectancy after diagnosis of HD [32]. No approved treatments exist that can cure, slow, or reverse the course of HD. Based on the results of the nonclinical studies, WVE-003 has promise as a disease-modifying agent for the treatment of patients with HD. Target engagement was demonstrated both in vitro and in vivo. Nonclinical studies conducted in rats and monkeys yielded no toxicologically meaningful findings that would prevent initiation of clinical studies in HD patients. [redacted]

2.3 Current Status of the Study and Dosing Paradigms as Recommended by the DEC and SMC

This is an adaptive study designed to evaluate data in an ongoing fashion to select and optimize dose levels and dosing frequencies. Data from Period 1 (SAD) have been reviewed by the DEC and SMC in accordance with Section 4.4.1 and Section 4.4.2, respectively, and recommendations were made regarding the number of cohorts, number of patients per cohort, and dose levels for Period 1 and P2C1.

In Period 1, the DEC/SMC have recommended dose escalation up to 90 mg. Initially, each cohort included 6 patients; however, due to variability in mHTT among patients, in [redacted], the DEC/SMC further recommended to expand each of the 3 single-dose cohorts to the cohort sizes listed below. Optional follow-up visits (up to 24 weeks postdose) were also added to provide the opportunity to obtain additional plasma and follow-up imaging samples prior to participation in Period 2. These additional data will be used to optimize the dose level:

- P1C1: 30 mg (n = 18; 2:1 active:placebo)
- P1C2: 60 mg (n = 18; 2:1 active:placebo)
- P1C3: 90 mg (n = 12; 2:1 active:placebo)

As of [redacted] the DEC/SMC recommended initiation of P2C1 with 30 mg administered Q8W through Week 16.

Subsequent dose levels, frequencies, number of cohorts, and number of patients per cohort will be determined based on DEC/SMC review of data from prior cohort(s [redacted] Section 4.4.1.3 [redacted]

3 STUDY OBJECTIVES

Primary Objective:

- To evaluate the safety and tolerability of WVE-003 in patients with HD

Secondary Objectives:

- To characterize the PK of WVE-003 in plasma
- To characterize the concentration of WVE-003 in CSF

Exploratory Objectives:

- To evaluate the PD effect of WVE-003 on the levels of mHTT protein in CSF
- To evaluate the effect of WVE-003 on clinical measures of disease including the Unified Huntington's Disease Rating Scale (UHDRS) and Short Problem Behaviors Assessment (PBA-s)
- To evaluate the PD effects of WVE-003 on relevant biomarkers in CSF, plasma, and peripheral blood mononuclear cells (PBMCs) (e.g., levels of wtHTT protein, total huntingtin [tHTT] protein in CSF, and neurofilament light [NfL] in CSF and plasma)
- To evaluate changes from baseline in magnetic resonance imaging (MRI) of the brain

4 STUDY DESIGN

4.1 Study Design Overview

This is a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of WVE-003 in adult patients with early-manifest HD who carry a targeted SNP rs362273 (SNP3).

To participate in the study, patients must undergo prescreening to confirm they are heterozygous for SNP3 with the A variant on the same allele as the CAG triplet expansion. Prescreening can happen any time before Screening. The prescreening testing process to confirm the presence of SNP3 is expected to take up to 6 weeks. If patients meet these criteria, they will continue to the Screening visit. The prescreening assessment will have a separate informed consent form (ICF).

The study will include 2 distinct periods: Period 1 to evaluate SAD cohorts and Period 2 to evaluate MAD cohorts of WVE-003. Patients may participate in Period 1 (SAD) and Period 2

(MAD) or Period 2 (MAD) only. All patients enrolled in Period 1 cohorts will have the opportunity to receive multiple doses in Period 2.

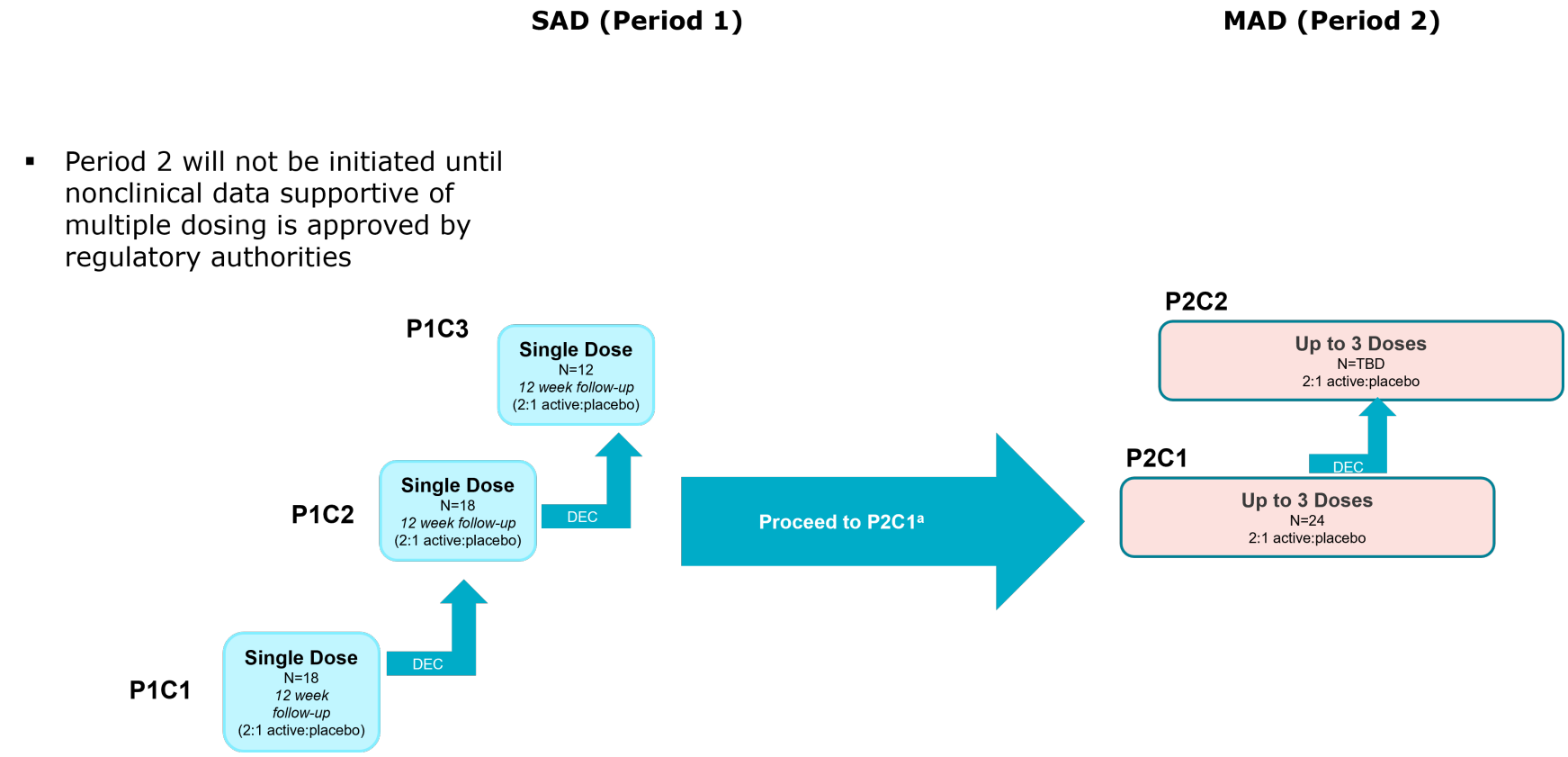
Cohorts in both Period 1 and Period 2 will be enrolled and dosed in a sequential manner. Subsequent SAD or MAD cohorts will not initiate until the requirements for dose escalation are met (Section 4.4.1.1). This study will utilize both a DEC and a SMC. The DEC will be responsible for making recommendations regarding dose escalation in Period 1, initiation of multiple dosing in Period 2, and subsequent dose escalation in Period 2. Recommendations made by the DEC will be reviewed by the independent SMC. Details regarding DEC and SMC reviews to determine dose escalation for subsequent cohorts in both Period 1 and Period 2 are provided in Section 4.4.1. Treatment-emergent adverse events (TEAEs) that meet the Stopping Criteria will be reviewed by the unblinded SMC (Section 4.4.3.1). In addition, the SMC will review unblinded, aggregate safety data (Section 4.4.2).

WVE-003 will be administered intrathecally in a volume of 20 mL of aCSF.

A schematic of the overall study design and timing is provided in Figure 1.

Of note, specific instructions regarding Coronavirus Disease 2019 (COVID-19) considerations are provided in Section 4.4.5.

Figure 1 Schematic of Study Design



- Period 2 will not be initiated until nonclinical data supportive of multiple dosing is approved by regulatory authorities

Abbreviations: DEC = Dose Escalation Committee; MAD = multiple ascending dose; PxCx = Period x Cohort x; Q8W = every 8 weeks; SAD = single ascending dose; SMC = Safety Monitoring Committee; TBD = to be determined.

[a] DEC/SMC review of data from P1C1 (n = 11; 30 mg), P1C2 (n = 6; 60 mg), and P1C3 (n = 6; 90 mg) [redacted].

Note: DEC recommendations will be reviewed by the SMC.

Dose and cohort size may be modified following recommendations from the DEC and SMC. [redacted], planned cohort sizes and dose levels in Period 1 are as follows: P1C1 (n = 18; 30 mg), P1C2 (n = 18; 60 mg), and P1C3 (n = 12; 90 mg). The planned cohort size and dose level for P2C1 is approximately n = 24; 30 mg Q8W.

4.1.1 Prescreening Phase

All patients must undergo a Prescreening visit to determine that they have heterozygosity at SNP rs362273 (SNP3) with the A variant only on the same allele as the CAG triplet expansion. Eligibility is determined by evaluation of a blood sample, as described in Section 8.1. A blood sample may be collected at the Prescreening visit. Alternately, a blood sample collected previously for another HD study being conducted by the Sponsor may be used to determine eligibility. Patients must sign a prescreening ICF prior to collection of the sample or evaluation of a previously collected sample. The testing process is expected to take up to 6 weeks. Prescreening can happen any time before Screening. Patients should not undergo any Screening assessments until it is confirmed that they are eligible based on these criteria. If patients meet these criteria, they will continue to the Screening Phase.

4.1.2 Screening Phase

The Screening period is intended to allow determination of patient eligibility for the study. It will begin when the study informed consent is signed. The ability of the patient to understand the consent form will be documented in the study ICF.

The Screening period will last up to 4 weeks. The required screening evaluations are outlined in the Schedule of Assessments (Section 4.2). Screening assessments can occur on multiple days, provided they are within the Screening period. The Investigator will determine whether patients meet the eligibility criteria and will collect the demographic and medical data permitting full characterization of the patient. Please refer to Section 4.4.5 regarding specific considerations as related to the COVID-19 pandemic.

Although this study is in early manifest disease, and therefore significant cognitive decline is not anticipated, it is important to demonstrate that patients are capable of understanding the information provided in the informed consent, and this needs to be documented in the source documents. The screening questionnaire provides documentation of whether the Investigator assessed if the patient is able to provide responses to the following domains: mental capacity, patient's previous psychiatry history, and patient's current psychiatric care.

Patients will be screened prior to Period 1 (Table 1). Alternately, new patients enrolled directly into Period 2 will be screened prior to dosing in Period 2 (Table 3).

Patients who fail the screening may be rescreened, as appropriate, in consultation with the Medical Monitor and when approved by the Sponsor. If a patient is rescreened within 1 month of the screening window, the MRI does not need to be repeated. A record of patient screen failures will be maintained for patients who do not qualify for enrollment, including the reason for the failure.

A study partner is not required to participate in this study. However, if a patient will be attending most clinical visits with a study partner, this person should be identified during the Screening

phase. This person may provide additional information on the PBA-s assessment throughout the study (Section 8.7.2).

4.1.3 Period 1 (Single-ascending-dose Period)

4.1.3.1 Period 1 Treatment

Period 1 will evaluate SAD cohorts of WVE-003. Eligible patients will be randomly allocated to either active or placebo treatment at the Baseline Visit. Patients will receive a single IT treatment. The planned Period 1 dose cohorts were as follows. Dose and cohort sizes were modified following recommendations from the DEC and SMC (details provided in Section 2.3).

- P1C1: 6 patients (2:1 active:placebo); 30 mg
- P1C2: 6 patients (2:1 active:placebo)

If the DEC or the Sponsor determines additional single-dose data are required prior to initiating Period 2, subsequent SAD cohorts may be conducted.

Within 1 week prior to performing the lumbar puncture, a blood sample will be tested locally for platelet count and prothrombin time to confirm that it is safe to proceed with the lumbar puncture. Other predose assessments may also be performed up to 1 week prior to dosing as specifically listed in Table 1, including UHDRS, PBA-s, and weight.

The first 2 patients (1:1 active:placebo) in Period 1 will be dosed and observed for 2 days in the clinic. If neither of these sentinel patients experiences a serious adverse event (SAE) during that period and the Single Dose Stopping Criteria (Section 4.4.3.1) are not met, the remaining patients will be dosed sequentially. If either of these events occur, the safety data will be reviewed by the SMC to determine the next steps (Section 4.4.2). Subsequent patients will be observed in the clinic for 1 day after dosing. Immediately after study drug administration, all patients should be ambulatory and active for approximately 30 minutes postdose. The Investigator should note any weakness or fatigue during this period. Formal physical examinations targeting the neurological system will be performed postdose at the time points specified in Table 1.

The SAD cohorts will be conducted in a sequential manner. Subsequent SAD cohorts will not initiate until the criteria for dose escalation are met (Section 4.4.1.1).

4.1.3.2 Period 1 Follow-up

All patients are required to complete follow-up assessments, including evaluations of safety, PD, PK, clinical effects, and MRI (Table 1). Patients will be followed up for a minimum of 12 weeks and up to 24 weeks postdose. Any postdose SAEs will be monitored until resolution.

Prior to being enrolled into Period 2, patients will continue to attend monthly follow-up visits through Week 24. After Period 2 initiation (Section 4.1.4), patients can proceed to multiple

dosing in Period 2 if the Period 1 Week 12/Day 85 visit has been completed. All patients must complete the Period 1 Week 12/Day 85 visit to ensure a sufficient washout of study drug prior to beginning treatment in Period 2 (multiple-dose period).

Visits on Weeks 16, 20, and 24 only need to be completed if the multiple-dose portion (Period 2) of the study has not initiated by the time the patient has reached Week 12/Day 85. At any point after Week 12/Day 85, the patient may roll over to Period 2 once initiated.

Any patient who completed Week 12/Day 85 may be asked to return for the next applicable Period 1 visit according to their number of days postdose. If a patient is past Week 24/Day 169, they may be asked to return for the assessments outlined on the Week 24/Day 169 visit.

Patients do not need to complete the visits on Weeks 16, 20, or 24 to be eligible for participation in Period 2.

4.1.4 Period 2 (Multiple-ascending-dose Period)

Period 2 will not be initiated until this Substantial Amendment to the IMPD with the supportive nonclinical data is approved by the local regulatory authorities. Following this approval, the Sponsor intends to initiate Period 2. The Sponsor will communicate this approval (in writing) directly to the study sites.

[redacted] the DEC/SMC recommended that Period 2 can initiate at a dose level of 30 mg Q8W.

4.1.4.1 Period 2 Assessment of Continued Patient Eligibility

Before initiation of Period 2, the Investigator should confirm patient eligibility to continue in the study (Section 4.2). If any clinically significant medical findings are observed that, in the judgment of the Investigator (and in consultation with the Sponsor), would make the patient unsuitable for continued participation in the study and/or completion of the study procedures, the patient may not be allowed to participate in Period 2. Applicable evaluations and tests from the last in-clinic visit in Period 1 may be used if the last in-clinic visit occurred within 4 weeks prior to the Confirm Eligibility visit for Period 2. Patients who are considered eligible and have completed at least through Period 1 Week 12/Day 85 may participate in Period 2. New patients will be screened for eligibility.

4.1.4.2 Period 2 Treatment Assignment

Patients in P2C1 will receive 30 mg WVE-003 or placebo administered Q8W. Approximately 24 patients will be enrolled in P2C1. Dose levels and cohort sizes for Period 2 subsequent cohorts will be determined by the DEC/SMC, based on previous Period 2 cohort data. Doses will be administered no more often than Q8W through Week 16 (maximum of 3 doses). [redacted]

All patients from Period 1 will have the opportunity to roll into Period 2 and will receive up to 3 additional doses of WVE-003 or placebo. Patients will not be re-randomized and will continue to receive active drug or placebo based on Period 1 treatment assignment. Patients will roll into the current Period 2 cohort, irrespective of Period 1 dose level.

Patients may be replaced in accordance with the requirements for dose escalation. Future DEC/SMC recommendations may include the addition of new Period 2 patients. All new patients in Period 2 will receive up to 3 doses of WVE-003 administered no more often than Q8W.

4.1.4.3 Period 2 Treatment

Within 1 week prior to performing any lumbar puncture, a blood sample will be tested locally for platelet count and prothrombin time to confirm that it is safe to proceed with the lumbar puncture. Other predose assessments may also be performed up to 1 week prior to dosing as specifically listed in Table 3 including UHDRS, PBA-s, and weight.

The Period 2 MAD cohorts will be conducted in a sequential manner. Subsequent multiple-dose cohorts will not initiate until the criteria for dose escalation are met (Section 4.4.1.3).

Immediately after study drug administration in any cohort, all patients should be ambulatory and active for approximately 30 minutes postdose on all dosing days. The Investigator should note any weakness or fatigue during this period. Formal physical examinations targeting the neurological system will be performed postdose at the time points specified in Table 3.

Patients will attend clinic visits Q4W for assessments of safety, PK, and PD. Patients in P2C1 will receive doses on Week 0, Week 8, and Week 16. Pending DEC/SMC recommendation, subsequent cohorts may receive doses Q8W or less frequently (e.g., on Week 0 and Week 12).

4.1.4.4 Period 2 Follow-up

All patients are required to complete follow-up assessments, including evaluations of safety, PD, PK, clinical effects, and MRI. Patients will be followed up for a minimum of 12 weeks after the last dose. Any postdose SAEs will be monitored until resolution.

4.1.5 Early Termination Visit

If a patient withdraws from the study early, the patient should complete an early termination visit. Refer to Section 5.3 for information on early withdrawal from study drug or from the study.

4.2 Schedule of Assessments

The schedule of assessments for Period 1 is presented in Table 1. Detailed time points for select assessments in Period 1 are provided in Table 2.

The schedule of all assessments for Period 2 is presented in Table 3. Detailed time points for select assessments in Period 2 are provided in Table 4**.**

Of note, specific instructions regarding COVID-19 considerations, are provided in Section 4.4.5.

Table 1 Schedule of Assessments (Period 1)

	Pre-screen-ing[a]	Screening[b]	Double-blind Treatment (Single Dose)		Sentinel Patient Follow-up	Required Follow-up				Additional Follow-up Visits			ET
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10***	**11***	**12***	
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Baseline (Day -6 to Day 1)[c] Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D3 (48 ± 4 h postdose)**	**D15 (±2)**	**D29 (±2)**	**D57 (±3)**	**D85 (±5)**	**D113 (±5)**	**D141 (±5)**	**D169 (±5)**	
Prescreening patient informed consent form (ICF) signed	X												
Patient Study ICF Signed		X											
Screening Questionnaire		X											
Blood sample for Prescreening assays	X												
Inclusion/exclusion criteria		X											
Medical history and demographics		X											
Prior and concomitant medications		X	X[c,k]	X[k]	X[k]	X	X	X	X	X	X	X	X
Hepatitis (HBsAg, HCV)		X											
C-SSRS "Baseline/Screening"[d]		X											

	Pre-screen-ing[a]	**Screening[b]**	**Double-blind Treatment (Single Dose)**		**Sentinel Patient Follow-up**	**Required Follow-up**				**Additional Follow-up Visits**			**ET**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10***	**11***	**12***	
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Baseline (Day -6 to Day 1)[c] Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D3 (48 ± 4 h postdose)**	**D15 (±2)**	**D29 (±2)**	**D57 (±3)**	**D85 (±5)**	**D113 (±5)**	**D141 (±5)**	**D169 (±5)**	
C-SSRS "Since Last Visit"[d]			X[c]	X	X	X	X	X	X	X	X	X	X
UHDRS[d]		X	X						X			X	X
PBA-s[d]		X	X						X			X	X
Weight		X	X						X			X	X
Height		X											
Physical examination[e]		X	X[c]	X	X		X	X	X	X	X	X	X
Targeted postdose physical examination of motor effects[f]			X[c]										
Blood pressure and pulse[g]		X	X[c]	X	X	X	X	X	X	X	X	X	X
Temperature		X	X[c]	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[h]			X[c]									X	X
Serum pregnancy test[h]		X											
Drug screen		X											

	Pre-screen-ing[a]	**Screening[b]**	**Double-blind Treatment (Single Dose)**		**Sentinel Patient Follow-up**	**Required Follow-up**				**Additional Follow-up Visits**			**ET**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10***	**11***	**12***	
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Baseline (Day -6 to Day 1)[c] Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D3 (48 ± 4 h postdose)**	**D15 (±2)**	**D29 (±2)**	**D57 (±3)**	**D85 (±5)**	**D113 (±5)**	**D141 (±5)**	**D169 (±5)**	
Adverse event monitoring		X	X[c,k]	X[k]	X[k]	X	X	X	X	X	X	X	X
Pre-LP PT and platelet[i]			X			X	X	X	X				X[l]
12-Lead ECG		Refer to Table 2											
Clinical laboratory tests		Refer to Table 2											
Blood sample for PK and PD		Refer to Table 2											
Urine sample for PK		Refer to Table 2											
Serum sample for immunogenicity		Refer to Table 2											
CSF sample for safety, drug concentration, and PD		Refer to Table 2											
PBMC sample for biomarker analyses		Refer to Table 2											
3T MRI of the brain (without contrast)		X										X	X

	Pre-screen-ing[a]	Screening[b]	Double-blind Treatment (Single Dose)		Sentinel Patient Follow-up	Required Follow-up				Additional Follow-up Visits			ET
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10***	**11***	**12***	
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Baseline (Day -6 to Day 1)[c] Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D3 (48 ± 4 h postdose)**	**D15 (±2)**	**D29 (±2)**	**D57 (±3)**	**D85 (±5)**	**D113 (±5)**	**D141 (±5)**	**D169 (±5)**	
Study drug administration via IT injection[j]			X[c]										

Abbreviations: 3T = 3 Tesla; A = adenine; AE = adverse event; CAG = cytosine-adenine-guanine; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; EOS = end of study; ET = early termination; h = hour; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IT = intrathecal; LP = lumbar puncture; MRI = magnetic resonance imaging; PBA-s = Short Problem Behaviors Assessment; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PT = prothrombin time; SNP = single nucleotide polymorphism; SNP3 = SNP rs362273; UHDRS = Unified Huntington's Disease Rating Scale; W = week.

***** Visits on W16, W20, and/or W24 only need to be completed if the multiple-dose portion (Period 2) of the study has not initiated by the time the patient has reached W12/D85. At any point after W12/D85, the patient may roll over to Period 2 once initiated. Any patient who completes W12/D85 may be asked to return for the next applicable visit according to their number of days postdose. If a patient is past W24/D169, they may be asked to return for the assessments outlined on the W24/D169 visit.

[a] Prescreening must be performed to confirm heterozygosity at SNP3 with the A variant only on the same allele as the CAG triplet expansion. Prescreening can happen any time before Screening. It is anticipated that it will take up to 6 weeks to process the results of this testing.

[b] Screening assessments can occur on multiple days, provided they are within the 4-week Screening period.

[c] Noted predose/baseline procedures must be performed within 24 hours predose. All others can be performed up to 1 week prior to dosing. Postdose procedures should be performed as described for each assessment.

[d] The UHDRS, PBA-s, and C-SSRS should be completed prior to any other assessments.

[e] Physical examination includes (at a minimum) the head, eyes, ears, nose, and throat, as well as the respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic systems. Predose physical examination should be done on Day 1 prior to dosing.

[f] Targeted postdose physical examination to assess potential motor effects focuses on the neurologic system, with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation. This should be performed at 1 and 4 hours postdose (±15 minutes) on Day 1.

[g] Blood pressure (systolic and diastolic) and pulse will be measured ≤60 minutes predose and 4 hours (±15 minutes) postdose on Day 1 and once at all other noted visits. Patient must rest quietly for ≥3 minutes prior to measuring.

[h] Negative serum pregnancy test will be documented at Screening for female patients. Negative urine pregnancy test will be documented predose for female patients on Day 1.

[i] Blood sample will be tested locally for platelet count and prothrombin time pre-LP to confirm safe to proceed with the lumbar puncture.

[j] Immediately after study drug administration, patients should be active for approximately 30 minutes postdose.

[k] All patients will remain in the clinic and have AEs and concomitant medications recorded through 1 day postdose. In addition, 2 sentinel patients will remain in the clinic and have AEs and concomitant medications recorded throughout the 2-day postdose period.

[1] This assessment will be performed only if optional lumbar puncture is performed at ET.

Table 2 Detailed Time Points for Selected Assessments (Period 1)

Assessments	Screening	D1									D2	Sentinel Patient Fol/up D3	W2 (D15)	W4 (D29)	W8 (D57)	W12 (D85)	W16 (D113), W20 (D141)*	W24 (D169)*	ET
			Postdose																
		Pre-dose	30 m	1 h	2 h	4 h	6 h	0 to 4 h	4 to 8 h	8 to 24 h	24 h	48 h							
Window (±)		**4 h**	**5 m**	**15 m**	**15 m**	**30 m**	**30 m**	**2 h**	**2 h**	**2 h**	**2 h**	**4 h**	**2 d**	**2 d**	**3 d**	**5 d**	**5 d**	**5 d**	
CSF sample[a]		X											X	X	X	X			X[b]
Plasma PD		X											X	X	X	X	X	X	X
Plasma PK		X	X	X	X	X	X				X		X	X	X	X			X
Urine PK								X	X	X									
PBMC sample for biomarker analyses		X									X		X	X	X	X		X	X
ECG[c]	X	X		X	X	X					X						X	X	X
Serum sample for Immunogenicity		X												X					X
Clinical laboratory tests (full panel)[d]	X	X												X				X	X
Clinical laboratory tests (CBC, CRP, complement, and fibrinogen)				X		X					X	X							

Abbreviations: CBC = complete blood count; CRP = C-reactive protein; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; ET = early termination; h = hour; m = minute; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic(s); PK = pharmacokinetic(s); W = week.

*Visits on W16, W20, and/or W24 only need to be completed if the multiple-dose portion (Period 2) of the study has not initiated by the time the patient has reached W12/D85. At any point after W12/D85, the patient may roll over to Period 2 once initiated. Any patient who completes W12/D85 may be asked to return for the next applicable visit according to their number of days postdose. If a patient is past W24/D169, they may be asked to return for the assessments outlined on the W24/D169 visit.

[a] On Day 1, CSF sample will be collected approximately 15 minutes prior to study drug administration. At all noted time points, approximately 20 mL of CSF total should be collected. CSF samples must be tested locally for safety for the following parameters: total protein, glucose, and cell counts (white blood cell counts with differential) on all noted visits.

[b] This lumbar puncture is optional for patients who terminate early.

[c] Electrocardiogram recordings will be obtained in triplicate in the supine position after the patient has rested comfortably for ≥10 minutes. ECGs should be performed in triplicate. At time points when plasma PK is also being collected, the ECG should be performed first, and PK should be collected within 30 minutes after (and within the applicable postdose window).

[d] Parameters to be assessed are detailed in Table 6. Clinical laboratory safety baseline assessments will be performed up to 1 week prior to dosing. Note that these assessments also include CBC, CRP, complement, and fibrinogen.

Table 3 Schedule of Assessments (Period 2)

	New Patients Only		Rollover Patients	Double-blind Treatment[c] (Repeat Dose)						Follow-up			
	Pre-screen-ing[a]	Screen-ing[b]	Confirm Eligibility		New Patients Only								
Visit	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (EOS)**	
Week		**-4 to 0**	**-4 to 0**	**0**		**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day -28 to -1**	**Baseline (Day -6 to Day 1) Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D29 (±3)**	**D57 (±3)**	**D85 (±3)**	**D113 (±3)**	**D141 (±3)**	**D169 (±3)**	**D197 (±5)**	**ET**
Prescreening patient informed consent form (ICF) signed	X												
Screening Questionnaire		X											
Patient Study ICF Signed		X											
Blood sample for Prescreening assays	X												
Inclusion/exclusion criteria		X											
Medical history and demographics		X											
Prior and concomitant medications		X		X[c,l]	X[l]	X[c]	X[c]	X[c]	X[c]	X	X	X	X
Hepatitis (HBsAg, HCV)		X											

	New Patients Only		**Rollover Patients**	**Double-blind Treatment[c] (Repeat Dose)**						**Follow-up**			
	Pre-screen-ing[a]	**Screen-ing[b]**	**Confirm Eligibility**		**New Patients Only**								
Visit	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (EOS)**	
Week		**-4 to 0**	**-4 to 0**	**0**		**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Study Day (Visit Window, if applicable) **Event/Assessment**		**Day -28 to -1**	**Day -28 to -1**	**Baseline (Day -6 to Day 1)** **Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D29 (±3)**	**D57 (±3)**	**D85 (±3)**	**D113 (±3)**	**D141 (±3)**	**D169 (±3)**	**D197 (±5)**	**ET**
C-SSRS "Baseline/Screening"[d]		X											
C-SSRS "Since Last Visit"[d]			X[o]	X[c]	X	X[c]	X[c]	X[c]	X[c]	X	X	X	X
UHDRS[d]		X	X[o]	X					X		X		X
PBA-s[d]		X	X[o]	X					X		X		X
Weight[e]		X		X		X	X	X	X		X		X
Height		X											
Physical examination[f]		X	X	X[c]	X	X[c]	X[c]	X[c]	X[c]	X	X	X	X
Targeted postdose physical examination of motor effects[g]				X[c]			Dosing visits only						
Blood pressure and pulse[h]		X	X	X[c]	X	X[c]	X[c]	X[c]	X[c]	X	X	X	X
Temperature[e]		X	X	X[c]	X	X[c]	X[c]	X[c]	X[c]	X	X	X	X
Urine pregnancy test[i]				X[c]		X[c]	X[c]	X[c]	X[c]				X
Serum pregnancy test[i]		X	X										
Drug screen		X	X										

	New Patients Only		Rollover Patients	Double-blind Treatment[c] (Repeat Dose)						Follow-up			
	Pre-screening[a]	Screening[b]	Confirm Eligibility		New Patients Only								
Visit	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (EOS)**	
Week		**-4 to 0**	**-4 to 0**	**0**		**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day -28 to -1**	**Baseline (Day -6 to Day 1) Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D29 (±3)**	**D57 (±3)**	**D85 (±3)**	**D113 (±3)**	**D141 (±3)**	**D169 (±3)**	**D197 (±5)**	**ET**
Adverse event monitoring		X	X	X[c,l]	X[l]	X[c]	X[c]	X[c]	X[c]	X	X	X	X
Pre-LP PT and platelet[j]				X		X	X	X	X	X	X	X	X[m]
12-lead ECG	X	X		X[p]		X	X	X	X	X			X
Clinical laboratory tests	X	X	X	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]
Blood sample for PK and PD				X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]
Serum sample for immunogenicity				X[p]		X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]
CSF sample for safety, drug concentration, and PD				X[p]		X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]
PBMC sample for biomarker analyses				X[p]	X[p]	X[p]	X[p]	X[p]	X[p]			X[p]	X[p]
3T MRI of the brain (without contrast)		X		X[n]							X		

	New Patients Only		Rollover Patients	Double-blind Treatment[c] (Repeat Dose)						Follow-up			
	Pre-screening[a]	Screening[b]	Confirm Eligibility		New Patients Only								
Visit	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (EOS)**	
Week		**-4 to 0**	**-4 to 0**	**0**		**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Study Day (Visit Window, if applicable) **Event/Assessment**		**Day -28 to -1**	**Day -28 to -1**	**Baseline (Day -6 to Day 1)** **Dosing (Day 1)**	**D2 (24 ± 4 h postdose)**	**D29 (±3)**	**D57 (±3)**	**D85 (±3)**	**D113 (±3)**	**D141 (±3)**	**D169 (±3)**	**D197 (±5)**	**ET**
Study drug administration via IT injection[k]				X[c]			Dosing visits only[c]						
Study completion												X	X

Abbreviations: 3T = 3 Tesla; A = adenine; AE = adverse event; CAG = cytosine-adenine-guanine; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; EOS = end of study; ET = early termination; h = hour; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IT = intrathecal; LP = lumbar puncture; MRI = magnetic resonance imaging; PBA-s = Short Problem Behaviors Assessment; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time; SNP = single nucleotide polymorphism; SNP3 = SNP rs362273; UHDRS = Unified Huntington's Disease Rating Scale.

[a] Prescreening must be performed to confirm heterozygosity at SNP3 with the A variant only on the same allele as the CAG triplet expansion. Prescreening can happen any time before Screening. It is anticipated that it will take up to 6 weeks to process the results of this testing.

[b] Screening assessments can occur on multiple days, provided they are within the 4-week Screening period.

[c] Noted assessment must be performed within 24 hours predose. All others can be performed up to 1 week prior to dosing. Postdose procedures should be performed as described for each assessment.

[d] The UHDRS, PBA-s, and C-SSRS should be completed prior to any other assessments.

[e] Weight and temperature will be collected predose on dosing days and once at all other noted time points.

[f] Physical examination includes (at a minimum) the head, eyes, ears, nose, and throat, as well as the respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic systems. Predose physical examination should be done on the day of dosing.

[g] Targeted postdose physical examination to assess potential motor effects focuses on the neurologic system, with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation. This should be performed at 1 and 4 hours postdose (±15 minutes) on all dosing days.

[h] Blood pressure (systolic and diastolic) and pulse will be measured ≤60 minutes predose and 4 hours (±15 minutes) postdose on dosing days and once at all other noted visits. Patient must rest quietly for ≥3 minutes prior to measuring.

[i] Negative serum pregnancy test will be documented at Screening for new female patients in Period 2. Negative urine pregnancy test will be documented predose for female patients on dosing days.

[j] Blood sample will be tested locally for platelet count and prothrombin time up to 1 week prior to any LP to confirm safe to proceed with the lumbar puncture.

[k] Immediately after study drug administration, patients who are able should be active for approximately 30 minutes postdose. If the DEC decides to reduce dose frequency or number of doses (Section 4.4.1.3), patients will complete all study assessments at the noted visits, but may not receive study drug.

[l] All patients will remain in the clinic and have AEs and concomitant medications recorded through 1 day postdose.

[m] This assessment will be performed only if optional lumbar puncture is performed at ET.
[n] This MRI should be performed for rollover patients only. If the Period 1 Week 24/Day 169 visit was conducted <4 weeks prior to the Period 2 Day 1 visit, the MRI does not need to be repeated.
[o] Assessments from the last in-clinic visit in Period 1 may be used if the last in-clinic visit occurred within 4 weeks prior to the Confirm Eligibility visit for Period 2.
[p] Reference Table 4 for details regarding assessments and time points.

Table 4 Detailed Time Points for Selected Assessments (Period 2)

Assessment	New Patients Only	Roll-over Patients	D1							New Patients Only	W4 (D29)	W8 (D57)		W12(D85) and W16 (D113)						W20 (D141)	W24 (D169	W28 (D197)	ET
	Screen-ing	Confirm Eligibility								D2													
			Pre dose	Postdose								Pre-dose	Postdose (Dosing Visit Only)	Pre-dose	Postdose (Dosing Visit Only)								
				30 m	1 h	2 h	4 h	6 h	8 to 24 h	24 h		4 h	2 hr		30 m	1 h	2 h	4 h	6 h				
Window (±)			4h	5 m	15 m	15 m	30 m	30 m	2h	2h			1 h	4 h	5 m	15 m	15 m	30 m	30 m	3 d	3 d	3 d	
CSF sample[a]			X								X	X		X						X	X	X	X[b]
Plasma PD			X								X	X		X						X	X	X	X
Plasma PK			X	X	X	X	X	X		X	X		X		X	X	X	X	X	X	X	X	X
PBMC sample for biomarker analyses			X							X	X	X		X								X	X
ECG[c]	X[e]		X		X	X	X			X				X		X				X			X
Serum sample for Immunogenicity			X								X	X		X						X	X	X	X
Clinical laboratory tests (full panel)[d]	X[e]	X[e]	X								X	X		X						X	X	X	X
Clinical laboratory tests (CBC, CRP, complement, fibrinogen)					X		X			X													

Abbreviations: CBC = complete blood count; CRP = C-reactive protein; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; ET = early termination; h = hour; m = minute; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic(s); PK = pharmacokinetic; W = week.

[a] Predose on all dosing days, CSF sample will be collected approximately 15 minutes prior to study drug administration. At all noted time points, approximately 20 mL of CSF total should be collected. CSF samples must be tested locally for safety for the following parameters: total protein, glucose, and cell counts (white blood cell counts with differential) on all noted visits.

[b] This lumbar puncture is optional for patients who terminate early.

[c] Electrocardiogram recordings will be obtained in the supine position after the patient has rested comfortably for ≥10 minutes. At time points when plasma PK is also being collected, the ECG should be performed first, and PK should be collected within 30 minutes after (and within the applicable postdose window).

[d] Parameters to be assessed are detailed in Table 6. Clinical laboratory safety assessments will be performed up to 1 week prior to dosing on all dosing days. Note that these assessments also include CBC, CRP, complement, and fibrinogen.

[e] Assessments from the last in-clinic visit in Period 1 may be used if the last in-clinic visit occurred within 4 weeks prior to the Confirm Eligibility visit for Period 2.

4.3 Study Endpoints

Safety

Adverse events, concomitant medications, physical examinations including detailed neurological examination, vital signs, weight, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis), CSF safety evaluations, MRI of the brain, and Columbia-Suicide Severity Rating Scale (C-SSRS)

Pharmacokinetics

- Pharmacokinetic parameters of WVE-003 in plasma at predefined time points
- Concentration of WVE-003 in CSF at predefined time points

Pharmacodynamics

- Change from baseline in the level of mHTT protein in CSF
- Change from baseline in the level of tHTT protein in CSF
- Change from baseline in the level of wtHTT protein in CSF
- Change from baseline in the level of NfL in CSF
- Change from baseline in the level of exploratory biomarkers in CSF, plasma, and/or PBMCs

Clinical Effects

- Change from baseline in the UHDRS Total Functional Capacity (TFC)
- Change from baseline in UHDRS total motor score
- Change from baseline in the UHDRS independence scale
- Change from baseline in Symbol Digit Modalities Test (SDMT)
- Change from baseline in Stroop word reading test
- Change from baseline in the composite UHDRS
- Change from baseline in the PBA-s
- Changes from baseline in MRI of the brain

4.4 Safety Considerations

4.4.1 Dose Escalation Committee Review

The DEC will be responsible for making recommendations regarding dose escalation in Period 1, initiation of multiple dosing in Period 2, and subsequent dose escalation in Period 2. The DEC will review blinded data. All recommendations of this committee will be reviewed by the SMC, which makes the final recommendation.

4.4.1.1 Period 1 – Dose Escalation

After all patients in a Period 1 cohort have received study drug and completed 2 weeks of postdose follow-up, the DEC will review the available blinded safety and PK data. The DEC will determine if it is safe to proceed with the next single-dose cohort. Based on data review, the DEC may decide to add additional cohorts or select alternate dose levels for any of the cohorts. [redacted]

4.4.1.2 Initiation of Period 2

The DEC will review the available safety and PK data and decide if Period 2 (i.e., P2C1) can be initiated. **Note that Period 2 will not be initiated until this Substantial Amendment to the IMPD with the supportive nonclinical data is approved by the local regulatory authorities.**

4.4.1.3 Period 2 – Subsequent MAD Cohorts (P2C2 and P2C3)

Once 6 patients in the current cohort have received at least 2 consecutive doses, the DEC will review the available blinded safety and PK data and determine if it is safe to proceed with the subsequent multiple-dose cohort. Based on data review, the DEC may decide to add additional cohorts, select alternate dose levels (including lower doses), reduce the number of doses or reduce the frequency of dose administration for any of the cohorts, or change the number of patients planned for a cohort. [redacted]

4.4.2 Safety Monitoring Committee Review

In addition to reviewing the DEC's decisions, the SMC will review unblinded aggregate safety data periodically and on an ad hoc basis throughout the study. The SMC will review any SAEs that occur in sentinel patients in order to determine if the cohort should continue or if a lower dose should be selected. In addition, if TEAEs occur that meet the Stopping Criteria, the SMC will review the unblinded safety data and determine whether it is safe to proceed with the cohort or if a lower dose should be explored.

If the stopping criteria are met at any point in the study, enrollment and dosing will be suspended until the data are reviewed. Similarly, if an SAE occurs in the sentinel patients in a cohort, no additional patients will be dosed in that cohort until the safety data are reviewed. Details on communication of safety concerns are detailed in Section 4.4.4.

4.4.3 Stopping Criteria

4.4.3.1 Single Dose Stopping Criteria (Cohort Stopping Criteria)

During Period 1, dosing of patients in a cohort will be suspended:

- If a single patient experiences an SAE assessed as related to study drug;
- If 2 patients experience a severe TEAE that is assessed as related to study drug; or
- If 4 patients experience a non-serious moderate or severe TEAE within the Medical Dictionary for Regulatory Activities (MedDRA) High Level Group Term (HLGT) *Spinal cord and nerve root disorders*, assessed as related to study drug.

Notification of dose suspension for a given cohort will be made in accordance with applicable regulations. If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations (e.g., substantial amendment) prior to restarting treatment.

4.4.3.2 Period 2 Stopping Criteria

During Period 2, either of the following will result in a dosing halt within the cohort and trigger assessment by the SMC to decide the safe dose level in Period 2:

- If 2 patients in a cohort experience an SAE assessed as at least possibly related to study drug.
- If 2 patients in a cohort experience a non-serious severe TEAE assessed as at least possibly related to study drug.

In addition, dosing will be stopped in any ongoing higher dose cohorts if the stopping rule is met in a lower-dose Period 2 cohort.

Notification of dose suspension for a given cohort will be made in accordance with applicable regulations. If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations (e.g., substantial amendment) prior to restarting treatment.

4.4.3.3 Individual Stopping Criteria

Dosing will be stopped for an individual patient at any time in the study if:

- A patient experiences a serious or intolerable adverse event (AE) that, in the Investigator's opinion, requires study drug discontinuation.

- A patient experiences a TEAE that is severe in intensity and related to administration of WVE-003 (except TEAEs associated with lumbar puncture).

The patient will be followed up for safety per protocol. Per the Investigator's judgement, the patient may be allowed to resume participation in the study if or when the event has resolved]. Dosing may be resumed for individual patients upon recovery from the severe event and if supported by the Investigator, based on their assessment of the benefit/risk balance for the patient.

4.4.3.4 Adverse Events That are Exempt from Stopping Criteria

Intrathecal administration of drugs is known to result in untoward effects such as post-lumbar puncture headache, pain, etc.[33,34] Given the common occurrence of such side effects following lumbar puncture, it is anticipated that patients may experience AEs temporal to the IT administration procedure that are not attributable to study drug[33,34]. Therefore, the AE terms listed in Table 5 will be exempted from the assessment of Stopping Criteria:

Table 5 Adverse Event Preferred Terms Exempted From Stopping Criteria

Preferred Terms Exempt From Stopping Criteria	
Administration site bruise	Instillation site bruise
Catheter site bruise	Post-lumbar puncture syndrome
Infusion site bruising	Post-procedural discomfort
Infusion site discomfort	Post-procedural contusion
Infusion site pain	Procedural headache
Injection site bruising	Procedural pain
Injection site discomfort	Traumatic lumbar puncture
Injection site pain	

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term.
Note: AEs exempted from the Stopping Criteria include the MedDRA PTs listed above and their associated verbatim terms.

While these procedural events are exempt from Stopping Criteria review, they will be recorded as AEs as described in Section 9. In addition, as part of their ongoing review of unblinded safety data, the SMC will carefully review the above-referenced exempted AE terms to ensure there are no meaningful imbalances between treatment groups.

4.4.4 Communication of Emergent Safety Concerns

Enrollment to the study will be closely monitored by the Sponsor. If the stopping criteria are met at any point in the study, enrollment and dosing will be suspended until the data are reviewed by the SMC. Notification of dose suspension for a given cohort will be made in accordance with applicable regulations. If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations (e.g., substantial amendment) prior to restarting treatment. Similarly, if an SAE occurs in the sentinel patients in a cohort, no additional patients will be dosed in that cohort until the safety data are reviewed. The Sponsor and/or contract research organization (CRO) will inform all sites in writing if enrollment and/or dosing is suspended. In addition, if enrollment is suspended, the interactive response technology (IRT) system will be adjusted such that no patients can be randomized to treatment until the safety review has been completed and a decision has been made to resume enrollment/dosing.

4.4.5 Considerations Due to COVID-19 Pandemic

Due to the continuing COVID-19 pandemic, it is possible that modifications to the planned schedules of assessments may be necessary in response to local mandates, site closures, quarantines, travel limitations, etc. In light of the serious and progressive nature of HD and the lack of any alternative treatment options for patients, the Sponsor believes that patients may continue to participate in the study and receive investigational treatment provided that appropriate safety monitoring can be performed to ensure patient safety and protocol requirements can be met to ensure the overall scientific integrity of data collection. The following guidelines should be followed to ensure compliance in situations where trial conduct may need to be modified in response to the COVID-19 pandemic:

Screening Activities: Screening activities may continue as long as local and institutional guidelines permit and if the protocol can be followed using the protocol-allowed visit windows. If this cannot be achieved, sites should temporarily halt screening new patients until local and institutional restrictions have been lifted.

Informed Consent Forms: If the ICF cannot be signed in person due to COVID-19 restrictions, or in the case of re-consent due to study changes, the Investigator may review the ICF via video or phone call to the patient. A copy of the signed ICF should be provided in person at the next clinic visit or by a secure process in accordance with site practices and local regulations. Record of informed consent should be filed in the medical record. If a signed copy of the form cannot be obtained from the patient, the ICF should be reviewed in the presence of an impartial witness (who is with the patient), and a witness attestation should be filed in the medical record. In the event a photograph of the ICF is used, an attestation should be made in the medical record by the person entering the form as to how the photograph was obtained.

Active Study Patients: Study dosing may continue as long as local and institutional guidelines permit, and safety monitoring is possible. If patients cannot be seen in clinic due to shelter-in place orders or institutional guidance, the Investigator should temporarily discontinue

administration of study drug and complete study visits that are amenable to remote or local assessments.

For study visits with assessments that can be performed locally, the Investigator should make every attempt to have a local laboratory perform the tests, or assess whether a home health service is available to collect samples at a patient's home by a trained nurse/phlebotomist.

If patients cannot attend their scheduled dosing visit, it is preferable to administer the missed dose if it can be safely administered at a subsequent time point.

All missed visits or changes to the study visit schedule outside of required visit windows due to COVID-19 should be noted as such in the electronic case report form (eCRF; Section 15.2.1). In addition, any changes to planned assessments due to the patient not being able to visit the clinic should be recorded as protocol deviations and marked "Due to COVID-19" (Section 15.3.2).

Vaccination: WVE-003 does not target the immune system, so immune response to COVID-19 vaccination is unlikely to be affected. Similarly, COVID-19 vaccination would not be expected to impact safety or efficacy of WVE-003. Investigators should consider the timing of dosing in the study with regard to timing of vaccination, when possible, so as to minimize the potential to confound interpretation of adverse events.

5 PATIENT SELECTION AND WITHDRAWAL CRITERIA

Approximately 54 patients will be enrolled. Patients will be randomized to a treatment arm/dose group only if they qualify according to all of the following inclusion and exclusion criteria. Patients will be required to be prescreened to determine heterozygosity at SNP3 with the A variant only on the same allele as the CAG triplet expansion.

During Screening, patients who do not meet all remaining inclusion/exclusion criteria will be considered screen failures. Patients who screen fail may be rescreened, as appropriate, in consultation with the Medical Monitor and when approved by the Sponsor.

5.1 Inclusion Criteria

1. Documented ability to understand the written study ICF(s) and consent and has provided signed written informed consent prior to any study procedures
2. Ambulatory male or female
3. Age ≥25 to ≤60 years old
4. Body mass index ≤32 kg/m^2
5. Documented CAG triplet repeats ≥36 in the *HTT* gene
6. Documented heterozygosity at SNP3

7. Documented presence of the A variant of SNP3 on the same allele as the pathogenic CAG triplet expansion

8. Clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4

9. UHDRS TFC scores ≥9 and ≤13

10. In the opinion of the Investigator, the patient is able to tolerate all study procedures, and is willing to comply with all other protocol requirements.

11. Willingness to practice highly effective contraception for the duration of the study and for [redacted] after the last dose of study drug, if patients or their partners are of childbearing potential. Non-childbearing potential and highly effective methods of contraception are defined in (Section 5.2.1.1 and Section 5.2.1.2). In addition, willingness to forego sperm or ova (egg) donation for the duration of the study and [redacted] months after completion of the study.

5.2 Exclusion Criteria

1. Malignancy or received treatment for malignancy, other than treated basal cell or squamous cell carcinoma of the skin, within the previous 5 years

2. Positive for Hepatitis B virus (HBV) or Hepatitis C virus (HCV).

3. Known to be positive for human immunodeficiency virus (HIV).

4. Clinically significant medical finding on the physical examination other than HD that, in the judgment of the Investigator, will make the patient unsuitable for participation in and/or completion of the study procedures

5. Previously received tominersen

6. Received prior treatment with viral or cellular-based gene therapy

7. Received any other study drug, including an investigational oligonucleotide, within the past 1 year or 5 half-lives of the drug, whichever is longer, with the exception of the following:

   a. Received WVE-120101 within the last 3 months (i.e., 5 half-lives); or

   b. Received WVE-120102 within the last 3 months (i.e., 5 half-lives)

8. Implantable CNS device that may interfere with ability to administer study drug via lumbar puncture or undergo MRI scan

9. History of substance abuse disorder (except nicotine) within 6 months prior to the Screening Visit

10. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit

11. Started or changed dose for concomitant medication for the treatment of HD symptoms or psychiatric disorders within 30 days prior to the Screening Visit (concomitant medications that have been administered on a stable regimen for ≥30 days are permitted)

12. Pregnant (as determined by a serum pregnancy test) or breast feeding at the Screening Visit, or plans to become pregnant during the course of the study

13. Clinically significant laboratory abnormality at Screening

14. Clinically significant abnormality at Screening ECG, including but not necessarily limited to a confirmed QT interval corrected for heart rate (QTc) ≥450 msec for males or ≥470 msec for females

15. Clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal, neurologic, malignant, metabolic, psychiatric, or other condition that, in the opinion of the Investigator, precludes the patient's safe participation in the study or would interfere with the study assessments. Mental status, psychiatric medical history, and eligibility for the study must be documented in the screening questionnaire.

16. Bone, spine, bleeding, or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture

17. Inability to undergo brain MRI (with or without sedation)

18. Deemed to be at significant risk for suicidal behavior based on any the following criteria:

a. The opinion of the Investigator

b. Answers "yes" to Actual Suicide Attempts or Suicidal Behaviors in the Suicidal Behaviors section of the C-SSRS with reference to a 2-year period prior to the Screening Visit

c. Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to the Screening Visit

d. Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS at the Baseline Visit since the last visit (Screening Visit)

19. Involved directly or indirectly in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study

20. History of hypersensitivity to other antisense oligonucleotides and any other drug that, in the opinion of the Investigator, may preclude study participation.

5.2.1 Additional Study Restrictions

As noted in the inclusion criteria, patients or their partners of childbearing potential must practice true abstinence or use highly effective methods of contraception. True abstinence is defined as refraining from heterosexual intercourse for the duration of the study. Non-childbearing potential and highly effective methods of contraception are defined in Section 5.2.1.1 and Section 5.2.1.2, respectively.

5.2.1.1 Non-Childbearing Potential

Non-childbearing potential is defined as a female who meets either of the following criteria:

- Postmenopausal state defined as no menses for 12 months without an alternative medical cause
- Documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy

5.2.1.2 Highly Effective Methods of Contraception

Contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods are defined as one of the following:

- True abstinence, defined as refraining from heterosexual intercourse for the duration of the study, when in line with the preferred and usual lifestyle of the patient
- Vasectomized partner (if that vasectomized partner is the sole sexual partner and has received medical assessment of the surgical success of the vasectomy)
- An intrauterine hormone-releasing system (IUS).
- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal combined)
- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- An intrauterine device (IUD)

In addition, male participants must be required to use a condom, as contraception requirement, for the duration of the study and, at minimum, until 5 months (i.e., 5 elimination half-lives) after the last WVE-003 dose.

Note that periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea are not acceptable methods of contraception.

5.3 Withdrawal and Discontinuation

Patients are free to withdraw from the study or discontinue treatment with study drug at any time upon request without prejudice to their future medical care by the Investigator or at the study site. Patient participation in the study may also be stopped at any time at the discretion of the Investigator or at the request of the Sponsor, as described in Section 5.3.1. Patients who withdraw or discontinue from study treatment will no longer receive study drug.

5.3.1 Withdrawal of Patients From the Study

Patients must be withdrawn from the study for any of the following:

- Patient's withdrawal of consent
- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Termination of the study by the Sponsor (see Section 14.4 for additional details)

In addition, the Sponsor may withdraw a patient from the study at their discretion and for any reason.

Any patient for whom consent to participate in the study is withdrawn will be removed from further treatment and study observation immediately upon the date of request. It should be encouraged that these patients complete the early termination study procedures (Section 4.1.5) and observations at the time of withdrawal. All information, including the reason for withdrawal from the study, must be recorded in the eCRF and source documentation.

5.3.2 Discontinuation of Study Drug

A patient must permanently discontinue treatment with study drug for any of the following reasons:

- The patient is withdrawn from the study (Section 5.3.1).

- The patient experiences a serious or intolerable AE (as defined in Section 9) that, in the Investigator's opinion, requires treatment discontinuation.

- A change in the patient's medical condition not consistent with the protocol requirements or that justifies withdrawal from the study or study drug

- Pregnancy (refer to Section 10)

- Patients with renal, hepatic, platelets, clotting time, and inflammatory laboratory values that are severe (i.e., CTCAE Grade 3) or higher and/or considered clinically significant, in the opinion of the Investigator, will temporarily discontinue treatment and be retested every 2 weeks until resolution of laboratory abnormalities. Patients with renal or hepatic laboratory values that are serious (i.e., CTCAE Grade 4) will be permanently discontinued from treatment and will be retested every 2 weeks until resolution.

If a patient discontinues treatment, they will be encouraged to remain in the study to be monitored and to complete all study-related procedures, unless consent is withdrawn. Patients who discontinue treatment due to an AE (Section 9) or pregnancy (Section 10) may require longer follow-up.

The reason for discontinuation of treatment with study drug must be recorded in the eCRF and source documentation.

5.3.3 Lost to Follow-up

Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. A minimum of 3 documented contact efforts should be made on different days over the course of 2 weeks. If the patient is unreachable by telephone, a registered letter will be sent to the patient requesting him or her to contact the study center. If contact with the patient is not established after all above attempts, this patient will be considered as lost to follow-up.

5.3.4 Replacements

Patients will be replaced in accordance with the requirements for dose escalation.

6 INVESTIGATIONAL DRUG AND PLACEBO

6.1 Method of Assigning Patients to Investigational Drug or Placebo

Patients who qualify according to all of the inclusion and exclusion criteria will be randomized into the study. Treatment will be assigned through randomization performed using a centralized, interactive voice/web response system.

6.2 Dose and Investigational Drug/Placebo Administration

6.2.1 Identity of Investigational Drug

6.2.1.1 WVE-003

WVE-003 will be provided as lyophilized powder for reconstitution and dilution for IT injection. WVE-003 for injection will be prepared by reconstituting and diluting the lyophilized powder with aCSF supplied by the Sponsor. Directions on reconstitution and dilution are provided in the Pharmacy Manual.

Laboratory Code: WVE-003

Chemistry: WVE-003 can be described chemically as the fully neutralized sodium salt of a 3′→5′ linked mixed 2′-*O*-(2-methoxyethyl)-/2′-deoxy-/ 2′-*O*-methyl ribonucleic acid oligonucleotide 20 mer, containing a prescribed combination of stereodefined *S*p and *R*p phosphorothioate diester, stereodefined *R*p *N*-(1,3-dimethylimidazolidin-2-ylidenyl) phosphoramidate diester, and phosphodiester internucleotide linkages.

International Nonproprietary Name: Not yet assigned

6.2.1.2 Placebo

Placebo will be aCSF provided by the Sponsor. It will be a sterile, preservative-free solution. Placebo will be visually identical in appearance to the WVE-003 injection solution and administered intrathecally in order to maintain the blind. Placebo will be administered in a volume of 20 mL.

6.2.2 Administration of Investigational Drug

Study drug (WVE-003 or placebo) will be administered by IT injection by direct lumbar puncture using an atraumatic needle, and the total volume of the injection will be 20 mL. WVE-003 will be diluted with aCSF provided by the Sponsor and administered in a volume of 20 mL, as described in the Pharmacy Manual. The lumbar puncture will be performed by a physician who is experienced in lumbar puncture procedure and drug administration and appropriately trained for the study. Within 1 week prior to the lumbar puncture, a blood sample will be tested locally for platelet count and prothrombin time to confirm that it is safe to proceed with the lumbar puncture (Section 8.2.8). Patients should not be sedated during administration of study drug. Imaging is allowed to guide lumbar puncture if needed. Detailed instructions on the procedure to be used for lumbar puncture are provided in the Study Operations Manual.

Within approximately 15 minutes prior to administration of study drug, CSF samples will be collected for safety assessments (Section 8.2.8), concentration of WVE-003 (Section 8.3), and PD (Section 8.4), per the Schedule of Assessments. Additional CSF collected will be stored and used for research purposes. Approximately 20 mL of CSF total should be collected**.**

Immediately after each administration of study drug, all patients should be ambulatory and active for approximately 30 minutes postdose. The Investigator should note any weakness or fatigue during this period. In addition, formal physical examinations targeting the neurological system will be performed at the time points noted in the Schedule of Assessments. Any postdose SAEs will be monitored until resolution.

6.3 Treatment Compliance

Provided that a patient attends the clinic visits, treatment noncompliance is not expected to be an issue. Thus, every attempt will be made to ensure regular visits by the patient to the clinic per the study schedule. Investigative staff will make every effort to contact patients who miss visits in order to obtain as much follow-up information as possible.

6.4 Management of Clinical Supplies

6.4.1 Investigational Drug Packaging and Storage

WVE-003 will be supplied by the Sponsor as a lyophilized powder in clear glass vials. Artificial CSF (placebo and diluent for WVE-003) will be supplied in single-use vials provided by the Sponsor for investigational use only.

All study drugs will be transported, received, stored, and handled in accordance with the container or product label, the instructions supplied to the pharmacy, relevant institution's Standard Operating Procedures (SOPs), and applicable regulations. Appropriate storage and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug.

Study drugs will be stored at 2ºC to 8ºC in a locked area accessible only to the pharmacy personnel until reconstitution. Both the WVE-003 for injection and aCSF placebo contain no preservatives and should be administered without delay or within 4 hours of reconstitution/preparation.

Partially used, unused, or damaged vials should be disposed according to Sponsor instructions.

Details on reconstitution and administration are provided in the Pharmacy Manual.

6.4.2 Study Drug Accountability

The Investigator will maintain accurate records of receipt of drug supplies, including dates of receipt. In addition, accurate records will be kept regarding when each treatment is administered, which patients received treatment, and the name of the personnel administering the treatment. Reasons for departure from the expected treatment regimen must also be recorded. Only trained site staff are permitted to treat study patients. A study monitor will review the accountability records.

6.4.3 Other Supplies

The study sites will be provided with the IB, Study Operations Manual, Pharmacy Manual, Imaging Manual, Laboratory Manual, laboratory kits, and other materials, as appropriate.

7 BLINDING AND RANDOMIZATION

7.1 Blinding

In order to maintain the blinding of the study drug (placebo or investigational product), all study personnel will be blinded to patient treatment assignment. Physicians, nurses, patients, and any study personnel performing patient assessments must NOT be informed of the patient's treatment assignment except in the event of a medical emergency or as required by regulatory authorities (Section 7.2).

The Sponsor and CRO staff directly responsible for the conduct of the study, the Investigator, and site staff will be blinded to treatment for the duration of the study until database lock.

The pharmacy personnel will be unblinded to prepare doses of investigational product or placebo to ensure that the patient and the clinical site staff responsible for administering study drug and conducting assessments per the protocol remain blinded to study treatment. In addition, a clinical research associate will be unblinded to perform drug accountability.

7.2 Breaking the Blind

7.2.1 Unblinding for Medical Emergency

A patient's treatment assignment should remain blinded until the end of the study. However, in the event of a medical emergency when the medical treatment of the patient depends on knowing the study treatment the patient received, the treatment blind may be broken through the IRT system. The Investigator must document the reasons for unblinding in the patient's source documents. *The Investigator is strongly advised not to divulge the patient's treatment assignment to any individual not directly involved in managing the medical emergency nor to personnel involved with the analysis and conduct of the study.*

7.2.2 Recording the Unblinding

If an unblinding occurs, the date on which the code was broken, together with the identity of the person responsible for breaking the blind, must be documented in the patient's source documents. The unblinded treatment information will not be disclosed to the Sponsor. In consultation with the Medical Monitor and the Sponsor, the patient may be withdrawn from the study, if the blind is broken.

The documentation should include, but is not limited to, the following information:

- Patient information

- Reason for unblinding
- Date and time of unblinding
- Name of the person requesting/responsible for unblinding

7.3 Randomization

Patients will be randomly allocated to either active or placebo treatment at their Baseline visit, in Period 1 if they enter in Period 1, or in Period 2 if they enter in Period 2. Patients who participate in both periods will receive the same treatment in Period 2 as they were randomized to receive in Period 1.

8 METHODS OF ASSESSMENT AND ENDPOINTS

8.1 Prescreening Assessments

Blood samples will be taken at the prescreening visit to enable patient eligibility assessment using a 2-step assay.

The assay will be validated and performed at Asuragen, Inc., Austin, Texas, or other subsidiary laboratories working under the Sponsor and Asuragen's close supervision. In step 1 of the assay, HD patient blood samples would undergo 2 independent allele-specific long-range polymerase chain reaction (AS LR-PCR) reactions. Each reaction has primer pairs specific to the SNP3 variant with nucleotides adenine (A) or guanine (G). Amplicons generated from each AS LR-PCR will proceed independently to step 2 of the assay. In step 2, CAG trinucleotide repeat length will be enumerated using Asuragen's AmplideX® PCR/capillary electrophoresis (CE) HTT Kit, which is based on repeat primed polymerase chain reaction (RP-PCR) technology and tested on a genetic analyzer within the terms of its CE mark. The amplicons from each reaction resultant from step 1 will be used for enumerating CAG repeat lengths on wtHTT and mtHTT alleles (also referred to as "phasing").

Only samples from AS LR-PCR with primer pair capable to amplify nucleotide "A" at SNP3 position and, when further analyzed in step 2, the amplicon is shown to be only mutant HTT allele with required CAG repeat length will be identified as phased eligible.

Patients confirmed to carry the A isoform of SNP3 on the same allele as the pathogenic CAG expansion will be qualified to undergo further screening for confirmation of eligibility. Investigators and patients will be advised only as to whether the patient meets the prescreening criteria and will not be provided with specific genetic test results (e.g., number of CAG repeats).

All blood samples will be sent to central laboratories for processing, analysis, and verification. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions on sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.2 Safety Assessments

The safety assessments will include the following:

- Adverse events (Section 9)
- Medical history and demographics
- Prior and concomitant medications
- Physical examination (including neurological and psychiatric)
- Height and weight
- Vital signs
- 12-lead ECG
- Clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis)
- Cerebrospinal fluid safety laboratory evaluation
- Suicidality assessment
- Pregnancy testing (if applicable)
- Drug screening

Any abnormal laboratory test results (hematology, clinical chemistry, or urine) or other safety assessments (e.g., vital sign measurements) that are clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

8.2.1 Medical History and Demographics

A general medical history will be obtained at the Screening Visit. Investigator assessment of past medical history at Screening will include information regarding any significant medical, surgical, psychiatric, and/or neurological conditions and treatments.

Prior HD treatments received, and other details about this condition will be recorded. In addition, education level will be recorded in accordance with the International Standard Classification of Education (1997).

Demographic data will be collected and summarized for each treatment group.

8.2.2 Prior and Concomitant Medications

Medications with a start date before the first dose of study drug will be classified as prior medications. Any medication that the patient began taking after the first dose of study drug will be classified as concomitant. Any medication that a patient started before the first dose of study drug and continued to take during the study will be classified as both prior and concomitant. Any medication that was stopped on the same day as the first dose of study drug will be considered a prior medication. If the stop date of a given medication is missing, then the medication will be classified as concomitant.

The minimum requirement is that the drug name, dose, indication, and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

8.2.3 Physical Examination

A complete physical examination will be performed at the time points noted in the Schedule of Assessments. The physical examination will include (but is not limited to) an examination of the head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic systems, and neurologic (including mental status, cranial nerves, motor system, reflexes, coordination and gait, and sensory system) systems.

At the postdose time points noted in the Schedule of Assessments, a targeted physical exam to assess potential motor effects will be performed. This exam will include a neurologic examination with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation.

Physical findings will be recorded in the eCRF and source documents.

8.2.4 Height and Weight

The patient's height and weight will be measured at the time points described in the Schedule of Assessments and recorded in the eCRF and source documents.

8.2.5 Vital Signs (Blood Pressure, Heart Rate and Temperature)

Vital sign measurements will be taken as per standard site practice, after the patient has been resting quietly (either lying flat or sitting, whichever is most appropriate for the condition of the patient) for a period of at least 3 minutes. Blood pressure (systolic and diastolic), temperature, and pulse will be measured by medically qualified personnel at the time points described in the Schedule of Assessments and recorded in the eCRF and source documents. As feasible, the same

position (either sitting or lying) should be used for all subsequent blood pressure measurements during the study for an individual patient. If the initial reading is high, the measurements will be repeated twice, and the average of the 3 readings will be used.

8.2.6 12-Lead ECG

Computerized, good quality, 12-lead ECGs will be collected and recorded at the time points described in the Schedule of Assessments. Recordings will be obtained in the *supine* position after the patient has rested comfortably for ≥10 minutes.

The ECG tracing will be submitted and read by a centralized reviewer (details will be provided in a study-specific manual). The following should be recorded on the trace and eCRF: whether the ECG is normal or abnormal and, if deemed abnormal, whether the abnormality is clinically significant or not clinically significant and note the abnormality.

8.2.7 Clinical Laboratory Evaluations

Clinical laboratory safety testing will be collected at the time points described in the Schedule of Assessments and recorded in the eCRF and source documents. Safety laboratory samples will be analyzed at a central laboratory. Local testing on these samples may be conducted as clinically indicated.

The parameters to be assessed are presented in Table 6. The full panel should include all parameters listed. Specific time points, as specified in the Schedule of Assessments, only require complete blood count (CBC), C-reactive protein (CRP), , complement, and fibrinogen.

Table 6 Clinical Laboratory Assessments

Hematology	Coagulation	Clinical chemistry	Urinalysis
Complete blood count, including: • White blood cell count (with differential when values are abnormal) • Red blood cell count • Hemoglobin • Hematocrit • Platelet count • Reticulocyte count • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration Measures of Inflammation, including: • High Sensitivity C-reactive protein • Complement • Fibrinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Creatine phosphokinase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Bilirubin	Urinalysis

8.2.8 Cerebrospinal Fluid Safety Laboratory Evaluation

A CSF safety laboratory sample obtained at the times noted on the Schedule of Assessments will be evaluated at a local laboratory. All CSF samples should be collected using an atraumatic needle. The following parameters will be assessed: total protein, glucose, and cell counts and differential per local laboratory specifications.

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for HD and stored for a maximum of 10 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions on sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.2.9 Suicidality Assessment (Columbia-Suicide Severity Rating Scale)

The C-SSRS is a measure of suicidal ideations and suicidal behaviors[35]. The C-SSRS, provided in the Study Manual, consists of 2 forms: a form measuring symptoms at Screening (baseline/screening version) that includes a lifetime history and a form measuring symptoms since the last study visit ("since last visit" version). The baseline/screening form will be performed at the Screening visit, and the "since last visit" form will be performed at all later time

points, as described in the Schedule of Assessments. A trained rater will complete this scale. The findings should be confirmed by the clinical opinion of the Investigator.
The Investigator should be notified if a patient responds "yes" to any of the questions. The Investigator will provide care according to local standards, which may include referral to specialists, medical treatment, or hospitalization as necessary.

8.2.10 Pregnancy Testing

For female patients of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit, and a negative urine pregnancy test must be documented at the times noted on the Schedule of Assessments. The serum pregnancy test will be determined by a central laboratory; urine pregnancy tests will be performed locally.

8.2.11 Drug Screening

A urine drug screen for opioids, cocaine, amphetamines, methadone, barbiturates, methamphetamine, and phencyclidine will be performed at the times noted on the Schedule of Assessments. Drug screen tests will be evaluated by a central laboratory.

8.3 Pharmacokinetic Assessments

Cerebrospinal fluid as well as plasma and urine samples for analysis of exposure to WVE-003 will be collected at the time points specified on Schedule of Assessments. Samples will be collected at the following time points:

Period 1 Plasma PK: Samples will be collected at all clinic visits during the Period 1 treatment phase. On Week 0/Day 1, samples will be collected predose (within 4 hours prior to dosing), and postdose at 30 minutes (±5 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±30 minutes), 6 hours (±30 minutes) and 24 hours (±2 hours) postdose. On all clinic visits (Week 2, Week 4, Week 8, and Week 12), samples will be collected. A sample will also be collected at the early termination (ET) visit, if the patient discontinues early.

Period 1 Urine PK: Samples will be collected on Week 0/Day 1 from 0-4 hours, 4-8 hours, and 8-24 hours postdose.

Period 1 CSF PK: Samples will be collected predose on Week 0/Day 1, as well as Week 2, Week 4, Week 8, and Week 12. A sample will also be collected at the ET visit, if the patient discontinues early.

Period 2 Plasma PK: At the first and last dosing visit, blood samples will be collected predose (within 4 hours prior to dosing), and postdose at 30 minutes (±5 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±30 minutes), and 6 hours (±30 minutes). New patients only will also have a sample collected on Day 1 at 24 hours (±2 hours) postdose. For any other dosing visit, blood samples will be collected at 2 hours (±1 hour) postdose. In addition, plasma PK samples will be collected once at all non-dosing clinic visits. A sample will also be collected at the ET visit, if the patient discontinues early.

Period 2 CSF PK: Samples will be collected at all clinic visits (Week 0/Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and Week 28). The sample will be collected predose on dosing visits. A sample will also be collected at the ET visit, if the patient discontinues early.

The date and time of the sample collection will be recorded.

Samples will be analyzed by a central laboratory to determine concentrations of WVE-003 using validated methods (plasma and CSF) or qualified methods (urine).

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for HD and stored for a maximum of 10 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.4 Pharmacodynamic Assessments

A CSF sample will be collected at the time points noted in the Schedule of Assessments to determine the change from baseline in concentration of mHTT protein. All CSF samples should be collected using an atraumatic needle. A plasma sample will be collected at the time points noted in the Schedule of Assessments (Section 4.2) to determine the change from baseline in concentration of NfL. In addition, the change from baseline in other measures of PD activity in CSF, plasma, or PBMCs will be assessed (e.g., tHTT, wtHTT, and NfL). Additional exploratory biomarkers (e.g., total tau) may also be evaluated.

The study may utilize the method described by Wild et al[36] or an alternative method to determine levels of mHTT protein.

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for HD and stored for a maximum of 10 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions on sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.5 Immunogenicity Assessments

Serum samples will be collected at the times noted on the Schedule of Assessments and analyzed at a central laboratory for measurement of anti-drug antibodies to WVE-003.

All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.6 Magnetic Resonance Imaging

A 3-Tesla MRI of the whole brain (without contrast) will be performed at the time points noted on the Schedule of Assessments. Sedation is permitted during the MRI.

The MRI will be assessed for safety purposes, in addition to exploratory structural assessments. Exploratory assessments will include, but are not limited to, volumetric assessments. Changes in MRIs of the brain will be characterized in patients receiving WVE-003.

The MRI will be performed by an appropriately trained individual. Detailed instructions on how the MRI will be performed and transferred to the central reader are provided in the Imaging Manual. The scans will be evaluated by a central reader.

8.7 Clinical Effects

8.7.1 Unified Huntington's Disease Rating Scale

The UHDRS is a research tool developed by the Huntington Study Group to provide a uniform assessment of the clinical features and course of HD[37]. The scale consists of 6 subtests, including motor assessment, cognitive assessment, behavioral assessment, an independence scale, functional assessment, and TFC, and is provided in the Study Manual. All subtests of the UHDRS should be performed except the behavioral assessment, as the PBA-s (Section 8.7.2) collects similar behavioral information.

The motor assessment evaluates motor features of HD with standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability. The total motor impairment score is the sum of all the individual motor ratings, with higher scores indicating more severe motor impairment than lower scores.

The cognitive assessment consists of a lexical verbal fluency test, SDMT, and the Stroop Interference test. The Stroop Test results are reported as the raw number of correct answers given in a 45-second period. Results for the other tests are reported as the raw number of correct responses. Higher scores indicate better cognitive performance.

The independence scale is used to follow disease progression in functional disability. The scale is rated from 100 (no special care needed) to 010 (tube-fed, total bed care).

The functional assessment checklist is a 25-question assessment that screens for capacity to complete the tasks mentioned in the assessment alone. The questions are asked in the presence of a family or friend to get the clinician's best judgment based on both responses. A response of "yes" is given a score of 1. A high score indicates better functioning.

The TFC is a brief interview involving the patient and a close family member or friend familiar with the patient's functioning. The measure has 5 items and addresses basic activities of living: occupation, handling finances, domestic responsibilities, activities of daily living (e.g., eating, dressing, bathing), and level of care.

8.7.2 Short Problem Behaviors Assessment

The PBA-s is a shorter version of the Problem Behaviors Assessment for HD (PBA-HD), a semi-structured interview designed to elicit information about behavioral symptoms relevant to HD. The shorter version was developed by the Behavioral Phenotype Working Group of the European Huntington's Disease Network (EHDN)[38].

The PBA-s contains 11 items, each measuring a different behavioral problem that is rated for both severity and frequency on a 5-point scale. Severity and frequency ratings are multiplied to provide an overall score for each symptom. The PBA-s is provided in the Study Manual.

Interviews are conducted with the patient. The final rating is determined by assessing all available information, including the interviewer's own observations of the patient's behavior. A study partner may also be interviewed as part of the PBA-s for this study if they are present at the visit.

9 ADVERSE EVENTS

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

Adverse event information will be collected beginning at enrollment (date of signed informed consent) and up to the end of the study. All ongoing AEs will be followed until ET or end of study (EOS), at a minimum, or until the Investigator and the Sponsor agree that further follow-up is not required. Requirements for SAE follow-up are detailed in Section 9.3.3.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the Investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

9.1 Eliciting and Documenting Adverse Events

All AEs reported or observed during the study, including AEs resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states, will be recorded on the AE page in the eCRF and in the site source notes. The eCRFs used to document AEs are designed to help ensure this information is collected in a standard way. Information to be collected includes event term, date and time of onset, date and time of resolution, Investigator-specified assessment of severity and relationship to study drug, action taken with respect to study drug, seriousness, any required treatment or evaluations, and outcome. All AEs will be followed until the ET or EOS visit, at a minimum. The sites will be provided with completion guidelines for the eCRF, which will further guide them on how to record the data, including AEs. The MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the patient signs informed consent but does not worsen should not be reported as an AE. However, if it worsens at any time during the study, it should be recorded as an AE. This includes any spontaneously reported worsening of depression, i.e., not based on the study rating scales.

In addition to observations of the patient, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are considered clinically significant will be documented on the AE page in the eCRF. Worsening of symptoms that are only detected on clinical effects rating scales will not be reported as AEs.

Adverse events will be assessed at each visit by direct questioning as well as elicited from physical examination by site staff. In addition, all sites in the study must ensure patients have a 24-hour telephone number to contact medical site staff for the duration of the study, in case of emergent AEs or SAEs.

If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

9.2 Definitions of Adverse Event Severity and Relationship to Study Drug

9.2.1 Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. Adverse event severity will be evaluated using the criteria in Table 7.

Table 7 Definitions of AE Severity Criteria

AE Severity	Definition
Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Moderate; of sufficient severity to make the patient uncomfortable; minimal, local, or noninvasive intervention indicated.
Severe	Severe or medically significant, of sufficient severity to cause the patient severe discomfort; may cause cessation of treatment; treatment of event symptoms/intervention may be required.

Abbreviation: AE = adverse event.

Changes in the severity of an AE should be documented in the eCRF to allow an assessment to be performed of the duration of the event at each level of intensity.

9.2.2 Relationship to Study Drug and/or Study Procedure

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process. All AEs, regardless of relationship, will be recorded in the eCRF. In addition, SAEs will be reported to regulatory authorities as required by local regulation (Section 9.3.4). In addition, the Investigator's assessment of an AE's relationship to study procedure should also be recorded.

The relationship or association of the study drug and/or study procedure in causing or contributing to the AE will be characterized using the classification and criteria presented in Table 8.

Table 8 Guidelines for Determining the Relationship (if Any) Between Adverse Event and the Study Drug and/or Study Procedure

AE Relationship	Definition
Definite	This relationship suggests that a definite causal relationship exists between treatment administration and the AE, and that other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.
Probable	This relationship suggests that a reasonable temporal sequence of the event with treatment administration exists and, based upon the known pharmacological action of the treatment, known or previously reported adverse reactions to the treatment or class of treatment, or judgment based on the Investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation of study drug.
Possible	This relationship suggests that the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of treatment administration or follows a known response pattern to the study drug, but could also have been produced by other factors.
Unlikely Related	This relationship suggests an improbable (but not impossible) association between the study drug and the reported event.
Not Related	This relationship suggests no association between the study drug and the reported event.

Abbreviation: AE = adverse event.

9.3 Serious Adverse Events

9.3.1 Serious Adverse Event Criteria

An SAE is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A life-threatening event does not include an AE that, had it occurred in a more severe form, might have caused death.

Serious AEs must be reported (Section 9.3.4) and will be followed up until resolution. Serious AEs that occur after the final follow-up visit need not be reported unless the Investigator considers them related to study drug.

The Sponsor will provide a Sponsor causality statement for all SAEs.

9.3.2 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE for which there is a reasonable possibility that the drug caused the event, and this SAE has not been previously identified as an expected/listed adverse event. A list of expected adverse events (if applicable) is provided in the current version of the IB and is considered the Reference Safety Information (RSI) for the study. Generally, the indication for which a product is intended would not be on the list of expected adverse reactions, but if it did occur, would not be considered "unexpected" for SUSAR reporting. As an example, a flare-up of symptoms consistent with the underlying disease under treatment that required hospitalization would constitute a serious adverse reaction; however, the event would not be considered unexpected. An exception would be if the reporter believed that study drug worsened the underlying condition.

9.3.3 Serious Adverse Event Follow-up

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs regardless of relationship to study drug will be followed by the Investigator until resolution. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

9.3.4 Serious Adverse Event Reporting

9.3.4.1 Reporting Requirements

Any AE that meets SAE criteria (Section 9.3.1) must be reported to the Sponsor and/or designee immediately (i.e., within 24 hours) after the site personnel first learn about the event using the SAE Report Form provided for the study. Regardless of causality, all SAEs that occur during the study (from the time the patient signs the ICF to the ET/EOS visit) must be reported to the Sponsor and recorded on the AE page of the patient's eCRF and in the patient's source documentation/medical file. Related SAE(s) that commence after the ET/EOS visit should be recorded in the patient's medical file and reported to the Sponsor but will not be added to the eCRF.

The initial report should include at least the following information:

- Study number
- Patient's identification number
- Description of the event

- Date and time of onset of the event
- Seriousness criteria
- Causality assessment to study drug

If follow-up is obtained or requested by the Sponsor and/or designee, the additional information should be emailed on an SAE Report Form to the Sponsor in a timely manner according to the procedures and timelines outlined above. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

The Investigator will be responsible for reporting all SAEs to the Institutional Review Board (IRB) or Ethics Committee (EC). The Sponsor will be responsible for reporting to the regulatory authorities and Central Ethics Committees, as per local requirements.

9.3.4.2 SAE Contact Information

Serious adverse event contact information is provided below.

[redacted]

[redacted]

North America

[redacted]

[redacted]

EMEA/APAC

[redacted]

[redacted]

9.4 Overdose

The study drugs are planned to be administered by trained study staff. Administration will be performed in accordance with the IB and instructions in a study-specific manual. Any incidence of overdose should be recorded as an SAE.

No clinical data are available regarding overdose with WVE-003. As with any agent, if overdose occurs, general supportive measures and close observation should be instituted. Misuse of the study drug for illegal purposes is not expected in this study as patients have no direct access to the study drugs.

10 PREGNANCIES

If a patient becomes pregnant during the course of the study, the pregnancy must be reported, and monitoring of the patient and child should be conducted until the pregnancy outcome.

If a female patient becomes pregnant during the study, she must be discontinued from the study drug although the patient may continue to be followed in the study. The Medical Monitor should be notified by the Investigator, and a Pregnancy Notification Form should be completed. The patient should be followed until the outcome of the pregnancy is known.

Pregnancy in and of itself is not an SAE. However, complications of the pregnancy should be reported to the Sponsor within 24 hours of knowledge by the Investigator (e.g., if the mother is hospitalized for dehydration), and an SAE form must be completed.

Based on the expected date of delivery, the Sponsor will attempt follow-up to determine the outcome of the pregnancy.

11 STATISTICAL METHODS

A separate statistical analysis will be performed for Period 1 (SAD) and Period 2 (MAD). Patients receiving placebo will be pooled to form a placebo control group for Period 1 and Period 2.

11.1 Sample Size Determination

The sample size was not calculated on the basis of statistical hypothesis testing; however, the number of patients is sufficient for a Phase 1b/2a assessment of safety, tolerability, PK, and early measures of PD and clinical effects.

11.2 Disposition of Patients

Screened patients are defined as any patient who signed informed consent. Randomized patients consist of all patients, with a signed informed consent, randomized via the IRT.

11.2.1 Analysis Populations

The following study populations will be evaluated:

- Safety population: randomized patients who receive at least 1 dose of study treatment.
- Pharmacokinetic population: the subset of the safety population with at least 1 postdose PK measurement
- Pharmacodynamic population: the subset of the safety population with at least 1 postdose PD measurement

- Clinical efficacy population: the subset of the safety population with at least 1 postdose measurement

11.3 Statistical Methods

Summary statistics (n, mean, standard deviation [SD], median, minimum and maximum values for continuous variables, and number [%] of patients in each category for categorical variables) will be provided by dose group and visit. Baseline for the Period 2 analysis of clinical effects and pharmacodynamic endpoints will be the measurement prior to the first dose of study drug in Period 2 for both new Period 2 patients and Period 1 rollover patients. Sensitivity analysis will include using the measurement prior to first dose in Period 1 for the Period 1 rollover patients.

11.3.1 Study Drug Exposure and Compliance

The extent of study drug exposure and compliance will be summarized by dose group for the safety population.

11.3.2 Analysis of Clinical Effects Endpoints

The change from baseline of the clinical effects endpoints will be analyzed using a mixed model for repeated measures (MMRM). The MMRM will include the relevant baseline measure and factor variables for time, dose group and time by dose group interaction. An unstructured variance-covariance matrix will be used to model the within-subject variability. If the MMRM with unstructured variance-covariance matrix does not converge, a compound symmetric structure will be used. Least square means of the time and dose group combinations and contrasts to placebo will be provided with 95% confidence intervals and p-values.

11.3.3 Analysis of Pharmacodynamic Endpoints

Pharmacodynamic biomarkers include (but are not limited to) mHTT, wtHTT, and NfL in the CSF and/or plasma. The NfL measurements will be log-transformed, and analysis will be based on the transformed data.

The MMRM described for the analysis of the clinical effects endpoints will be applied with the exception that the baseline measure will not be included.

11.3.4 Analysis of Safety Data

The summary of safety results will be presented by dose group. All safety analyses will be performed on the safety population using the following common rules:

- The baseline value is defined generally as the last available value before randomization.
- Adverse event observation periods are defined as follows:
    - Pretreatment AEs are AEs that developed or worsened prior to the first dose of study drug.

- On-treatment adverse events are AEs that developed or worsened from the first dose of study drug to study completion/discontinuation. Summaries of TEAEs will include all on-treatment AEs.

- For quantitative safety parameters based on central laboratory/reading measurement, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.

11.3.4.1 Adverse Events

Treatment-emergent AEs, TEAEs assessed as related to study drug or to study procedures, treatment-emergent SAEs will be summarized for each dose group based on MedDRA coding of verbatim terms reported by investigators.

Adverse event incidence tables will present, by SOC and PT, the number and percentage of patients experiencing an AE, the number and percentage of patients experiencing an AE by severity and by relationship to treatment.

Listings of all AEs, SAEs, deaths, and AEs leading to study discontinuation will be provided.

11.3.4.2 Clinical Laboratory Evaluations

Summary statistics of laboratory variables will be calculated for each visit or study assessment by dose group. Shift tables of change from baseline will be provided.

11.3.4.3 Other Safety Evaluations

Summary statistics of vital signs, ECG, and height and weight variables will be calculated for each visit or study assessment by treatment group. The C-SSRS will be summarized by study visit by treatment group.

Anti-drug antibody assay results to WVE-003 will be described categorically. Summary statistics for anti-drug antibody titer results will be provided.

11.3.5 Analysis of Pharmacokinetic Variables

The plasma and CSF WVE-003 concentration, and potentially WVE-003-related metabolite data will be summarized for patients in the PK population. Excreted urine amount over each collection interval and the total amount over 24 hours will also be summarized.

For each patient in the PK population, the plasma WVE-003 concentration data will be analyzed by noncompartmental PK analysis. The parameters listed in Table 9 will be determined. Additional PK parameters may be evaluated if deemed appropriate. Pharmacokinetic parameters for each dose group will be summarized for each WVE-003 dose level and each visit.

Table 9 Plasma Pharmacokinetic Parameters of WVE-003

Parameter	Definition
C_{max}	Maximum observed concentration
t_{max}	Time of occurrence of C_{max}
AUC_{last}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration

11.3.6 Interim Analyses

An unblinded interim analysis may be performed and the results summarized by dose group. The SAP will be finalized prior to the interim analysis.

An SMC (Section 14.1) will be assembled to review the safety, tolerability, PK, and PD activity. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to the SMC prior to each SMC meeting. Details on the safety assessments, frequency of review, meeting schedules, and controlled access to unblinded data are outlined in the SMC charter.

12 REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

12.1 Declaration of Helsinki

The Sponsor and Investigator(s) will ensure that this study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

12.2 Good Clinical Practice

The study will be conducted according to the study protocol and SOPs that meet the guidelines provided by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical studies and any other applicable local regulatory requirements.

12.3 Institutional Review Boards/Ethics Committees

Federal regulations and ICH guidelines require that approval be obtained from an IRB or EC before participation of human patients in research studies. Before study onset, the protocol, ICF, and advertisements to be used for the recruitment of study patients and any other written information regarding this study to be provided to the patient must be approved by the IRB or EC. The documentation of all IRB/EC approvals and of the IRB/EC compliance with ICH guideline E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/EC approvals should be signed by the chairman or designee and should identify the IRB/EC name and address, the clinical protocol by title or protocol number or both, and the date of approval or when the favorable opinion was granted. The study protocol, appendices, and ICFs must be approved by the IRB/EC.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/EC. The Investigator must promptly supply the Sponsor or its designee, the IRB/EC, and, where applicable, the institution with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

12.4 Informed Consent Forms

Signed ICFs in compliance with the Declaration of Helsinki, current ICH and GCP guidelines, US Title 21 Code of Federal Regulations (CFR) Part 50, and applicable local regulations will be obtained from each patient before enrolling the patient in the study or performing any unusual or nonroutine procedure that involves risk to the patient.

Informed consent form templates will be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF(s) must be reviewed by the Sponsor or its designee or both before IRB/EC submission. Once reviewed, the ICF(s) will be submitted by the Investigator to his or her IRB/EC for review and approval before the start of the study. If the ICF(s) is revised during the course of the study, all actively participating patients must sign the revised form.

Before Screening, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the appropriate ICF.

The Investigator will retain the signed original ICF(s) and give a copy of the signed original form(s) to the patient.

12.5 Privacy

The Sponsor and Investigator(s) will ensure that this study is conducted in accordance with the most recent version of the applicable privacy laws, including local privacy laws. Additional information on how the Sponsor handles privacy can be found at https://wavelifesciences.com/privacy/.

13 INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study in accordance with GCP guidance. These items may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/EC but will not result in protocol amendments.

13.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage

area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the Sponsor, its designee, applicable regulatory agencies, or the IRB/EC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.2 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to the following:

- IRB/EC approval
- A fully executed Clinical Study Agreement
- Curriculum vitae for the Investigator and each sub-investigator listed on the IRB/EC application
- Financial disclosure information, as applicable
- IRB/EC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient
- Laboratory certifications and normal ranges for any local laboratories used by the site

13.3 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers in accordance with all national, state, and local laws or regulations.

13.4 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

13.5 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the IRB/EC as appropriate.

13.6 Investigator's Final Report

When applicable, the Investigator should inform the institution of study completion; the investigator/institution should provide the IRB/EC with a summary of the study outcome and the Sponsor and regulatory authority(ies) with any reports required.

13.7 Records Retention

The Investigator/institution will retain essential documents until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, these documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

13.8 Publications

All information regarding WVE-003 supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use Sponsor's confidential information solely to accomplish the study and will not use such information for any other purposes without the prior written consent of the Sponsor. The Investigator is obligated to provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used toward the development of WVE-003 and may be disclosed by the Sponsor to regulatory authority(ies), other Investigators, corporate partners, and consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Committee/Clinical Advisory Committee will be formed (Section 14.4) to oversee any publication or presentation of the study results. Subsequently, individual Investigators may publish results from the study in compliance with their agreements with the Sponsor. A prepublication manuscript is to be provided to the Sponsor at least 45 days prior to the submission of the manuscript to a publisher.

14 STUDY COMMITTEES

14.1 Safety Monitoring Committee

An unblinded, independent SMC consisting of at least 3 members (including a statistician and 2 physicians of whom 1 must be a neurologist) will review unblinded, aggregate safety data

periodically. In addition, the SMC will review SAEs that occur in the sentinel patients and TEAEs that meet the stopping criteria. The SMC will also review dose recommendations from the DEC. Unblinded information will be reviewed in a closed session without the Sponsor present. Details on safety reviews are provided in Section 4.4.

Further details regarding the SMC, including committee membership, will be provided in a SMC Charter.

14.2 Dose Escalation Committee

The DEC will be responsible for making decisions regarding dose escalation in Period 1, selection of the initial dose level in Period 2, and subsequent dose escalation in Period 2. The DEC will review blinded data. This committee will include, but is not limited to, a Sponsor representative, a Medical Monitor, and a member of the Clinical Advisory Committee or Study Investigator. Details on safety reviews are provided in Section 4.4. Further details regarding the DEC, including committee membership, will be provided in a DEC Charter.

14.3 Clinical Advisory Committee

A Clinical Advisory Committee, consisting of a Study Investigator and experts in HD, will be formed to provide advice regarding protocol and study conduct.

14.4 Publications Committee

A Publications Committee, consisting of Investigators participating in the study, at least 1 member of the Clinical Advisory Committee, and representatives from the Sponsor as appropriate, will be formed to oversee any publication or presentation of the study results, which will reflect the experience of all participating study centers.

15 STUDY MANAGEMENT

15.1 Monitoring

15.1.1 Monitoring of the Study

Monitoring and auditing procedures developed by the Sponsor or designee will be followed in order to comply with ICH GCP guidelines.

During the study, a monitor from the Sponsor or designee will have regular contact with the study center for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being recorded accurately in the source documents and eCRFs, and that investigational product accountability checks are being performed

- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice and other records relevant to the study. Verification will require direct access to all original records for each patient (e.g., clinic charts) or as appropriate per local regulations.

- Record and report any protocol deviations not sent to the Sponsor or designee previously

- Confirm AEs and SAEs have been documented properly in the eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met the criteria for reporting (i.e., serious adverse drug reactions) have been forwarded to the IRB/EC

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2 Data Quality Assurance

15.2.1 Electronic Case Report Forms and Data Management

Patient data will be captured in an electronic data capture system, [redacted] provided by the Sponsor or designee. Data will be entered directly from the source documents to the eCRFs following the CRF Completion Guidelines. Source documents should be clear, complete, and accurate and should include all the details of study assessments performed per the protocol. The Investigator is responsible for ensuring that the data entered on the eCRFs are accurate and complete and all data are entered in a timely manner.

Any missed visits, changes to study visit schedule, etc. due to COVID-19 considerations should be noted as such.

The final eCRF data and audit trails will be archived in an electronic media and placed in the Investigator's study file.

15.2.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to all study records or as appropriate per local regulations. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or regulatory authorities access to all study records.

The Investigator should notify the Sponsor promptly of any audits scheduled by any regulatory authorities and should promptly forward copies of any audit reports received to the Sponsor.

15.3 Management of Protocol Amendments and Deviations

15.3.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol, other than minor clarifications and typographical corrections, must be submitted in writing to the Investigator's IRB/EC and regulatory authorities for approval before patients can be enrolled into an amended protocol.

15.3.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/EC. A major protocol deviation is any deviation that impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from the protocol to eliminate an immediate hazard to study patients without prior IRB/EC approval. As soon as possible after such an occurrence, the implemented deviation, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/EC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required. Any deviation from the study protocol that is due to COVID-19 considerations should be noted as such.

Protocol deviations will be documented by the clinical monitor in the clinical study management system and on monitoring reports throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. As required by local regulatory authorities, the Investigator will notify the IRB/EC of any applicable protocol deviations in a timely manner.

15.4 Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor may terminate the study or close an individual study site. Reasons for terminating a study or closing a site may include, but are not limited to, the following:

1. The research can no longer meet its stated scientific purpose, and this assessment has been confirmed by the medical ethical review committee, which has given a positive assessment of the research.

2. Severe noncompliance to this protocol as judged by the Investigator and/or the Sponsor

3. Due to unforeseen circumstances that prevent continuation of the research (e.g., financial issue)

The end of the study is defined as the date on which the last patient completes the last visit (includes follow-up visit).

Upon completion or termination of the study, the study monitor will conduct site closure activities with the Investigator or site staff (as appropriate) in accordance with applicable regulations, ICH GCP, and SOPs.

15.5 Final Report

Whether the study is completed or terminated prematurely, the Sponsor will ensure that a final report is prepared and provided to the regulatory agency(ies), as applicable. The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH Guideline E3: Structure and content of clinical study reports (CSRs).

In accordance with local regulatory requirements, a Principal Investigator will be identified for the approval and signoff of the clinical study report. The Principal Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

The Investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical study registers.

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